

PREPARATION OF FINE CHEMICALS AS USEFUL
DRUG INTERMEDIATES

THESIS SUBMITTED
UNIVERSITY OF MUMBAI

FOR THE DEGREE OF
MASTER OF PHARMACEUTICAL SCIENCES
IN
PHARMACEUTICAL CHEMISTRY

SUBMITTED BY
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UNDER THE GUIDANCE OF
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MUMBAI - 400 012

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A

Thesis Submitted

To

The University Of Mumbai

For The Degree Of

Master Of Pharmaceutical Sciences

In The

Faculty Of Technology

(Pharmaceutical Chemistry)

By

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STATEMENT

Statement submitted under rule 0.412

For the Thesis which I intend to submit, no degree or diploma or distinction has been conferred on me before, either in this or any other University.

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Statement I :

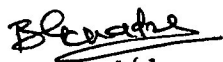
The work embodied in the Thesis to be submitted is original, based on the discovery of new facts.

The assessment of the compound has been made at the department of Chemotherapy, Haffkine Institute, Mumbai-400 012.

Statement II :

During the study, all available information of related nature published in scientific journals by previous workers in allied fields, has been used as a source of information, as indicated in the "References".

The entire work has been planned and carried out by the candidate.



Dr. B. G. Khadse
Signature of the Research Guide.



Sagar M. Agnihotri
Signature of the Research Student.

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Introduction

INTRODUCTION

Research could be defined as an orderly approach to the revelation of new knowledge about different sciences in the universe. The objective of research is to advance the frontiers of knowledge and understanding, and the boundaries of the search are limitless. Industrial research shares this quest for new knowledge, but its goals are ultimately far different from those of the academic researchers. In industry, the research goal is the knowledge applicable to the business needs of a company that will enable the company to participate in the forefront of new technology or lay the scientific foundation for the development of new products or processes. Though there is no precise demarcation between the definition of research (R) and development (D), i.e. R&D, yet a broad distinction can be made.

The purpose of research is to develop new knowledge, and the purpose of development is to apply scientific and engineering knowledge to develop reliable, high quality and useful products and processes. Basic research is REVOLUTIONARY and developmental research is EVOLUTIONARY. In general, development seeks to move product or process concepts through a series of definite stages to prove, refine, and ready them for commercial application.

The pharmaceutical industry is unique in that its success and failure, and consequently its survival, is critically dependent on its inputs into research, which feeds and determines the quantity and quality of its product pipeline. R&D in the industry thus influences the following important areas:

- 1) Product Development and Product Quality.
- 2) Reduction of Production Costs.
- 3) Keeping Pace with New Technology.

It is a well established fact that while the International pharmaceutical companies spend approximately 12-15% of their sales turnover on R&D, the Indian companies spend less than 2%. Needless to say, the increasing national and international competition changing world markets, the magic

mantra of liberalisation and globalisation, the enormous emphasis on high quality and low costs and the implications of the recently signed GATT treaty, will all combine to radically influence our attitude and approach to pharmaceutical R&D, both at the industrial and institutional level.

R&D Categories

R&D can be categorized into three types :

- 1) **INCREMENTAL R&D** : It involves the exploitation of existing scientific and engineering knowledge in new ways. It is characteristically low risk and offers modest reward. It has a very high probability of technical success (40-80%) and takes a short time for completion, typically 6-24 months. However, its competitive potential is modest and durability of competitive advantage is short lived. This is the type of R&D practised by most of the Indian pharmaceutical units and companies engaged in generic business abroad.
- 2) **RADICAL R&D** : It involves the creation of knowledge which is new to the company and probably new to the world, for a specific business objective. It is characterized by high risk and high reward. Its probability of technical success in early stages is modest, and it may take 2-7 years for completion. Its competitive potential is large and often protectable by patents, and thus durability of competitive advantage gained is quite long. This type of R&D includes finding new uses and routes of administration, as well as new methods to synthesize existing drugs. It may also include the modification of existing molecules, to optimize their efficacy and safety. This is practised by those companies which have well established R&D facilities and outstanding research scientists.
- 3) **FUNDAMENTAL R&D**: It is characterized by research, which is driven by the sole objective of gaining knowledge. Fundamental R&D creates knowledge new to the company and new to the world. It is characterized by high risk and uncertain applicability to business needs. Any commercial gain is not directly visible. Its success is very difficult to assess, because it

depends on the selection of a R&D concept. It involves very high expenditure, is open ended and consequently requires a lot of time. Its competitive potential is very large, and competitive advantages gained are also of long duration. This type of activity is primarily carried out in Universities and national institutions. Such projects are largely funded by government and private agencies. Industry may also collaborate with institutions in such research projects, at a stage when the chances of success are considerably improved, and the outcome of the research is of strategic interest to the concerned company.

INDIAN SCENARIO AND R&D STRATEGIES

The Indian pharmaceutical industry has made significant strides in the last 25 years, but its R&D efforts have concentrated on development of formulations and process improvement with the main objective of achieving self sufficiency and providing drugs at reasonable prices. Further, the protected market, the Indian Patent Act and government policies have not been conducive for conducting basic research. All this, however, is due to change with the signing of the GATT treaty. The situation demands that we evaluate our strengths and weaknesses and plan our short and long term R&D priorities and strategies. Two important areas which call for prompt strategic actions are :

- 1) Upgradation of present facilities and products to international standards.
- 2) Co-operative efforts to mobilize resources for new drug discovery and development¹.

Pharmaceutical industry in India is one of the most important sectors of Indian economy which is of crucial significance to the health of its people. To this end, therefore, the government has taken special efforts to make available standard quality drugs, especially the life-saving ones, at reasonable prices to everyone in the country. To achieve the goal of 'Health for all', the government has formulated a policy to produce drugs in bulk quantities and market them with a comparatively lower profit margin.

BULK DRUGS

In order to encourage the production of indigenously produced bulk drugs, the Government of India decided to adopt certain policies. Some of the points of reference of these policies were as follows:

- 1) Provide a leadership role to public sector drug companies and encourage growth of national sector of the drug industry.
- 2) Allow the Indian manufacturer licenses upto 10 times the value of their bulk drug production.
- 3) Channelise the activities of foreign drug manufacturing companies in accordance with national objectives and priorities.

These enlightened policies have borne good and satisfactory results. Most of the pharmaceutical houses which were importing finished products started manufacturing or developing imported intermediates.

BULK DRUG REQUIREMENTS

The phenomenal growth of bulk drug industry during the last two decades indicates the industry has a potential of expanding and meeting the future requirements of the country.

TECHNOLOGY

The technology employed in production and quality control is of the level employed in the industrialized countries in Western Europe and in U.S.A. This was made possible by the Indian government policy of allowing international collaboration where such assistance confer long term benefits to the Indian pharma-industry.

A purpose of this policy was that such collaboration should evolve a programme that would finally lead to indigenous self sufficiency in improving the existing technology. This would result in conservation of energy, better utilization of plant capacity, minimizing use of solvents and making the process safer.

RESEARCH AND DEVELOPMENT

The production of bulk drugs has been made sophisticated by research and development efforts. The R&D activities and allocation for the same are presently at a low level of around 1%. India needs to develop its R&D efforts at least at par with countries which are able to offer intermediates and basic drugs involving sophisticated technology. However this is possible only if industry is left with enough margins and surplus to develop R&D.

AVAILABILITY AND DEMAND

India produces about 400 Bulk drugs including those involving sophisticated technologies. The demand pattern for drug industry fluctuates rapidly depending on the availability of better substitutes. The average life of a drug is between 5 to 7 years, in most cases. However, demand estimates for each drug are drawn upon the basis of present rate of consumption.

The value of imports of bulk drugs rose steeply from Rs.10.50 crores in 1961 to Rs.113.81 in 1981 to Rs.150 crores in 1984 and is yet rising¹. Due to shortfall in production, the visualized demand can be met only by increasing the quantum of imports. Imports cannot be altogether stopped. Due to several restrictions like inadequate availability of indigenous raw materials, higher rate of duty on intermediates compared to that on the final product, underutilisation of the installed capacity, the entire drug production cannot be met by indigenous production alone. Newer and better drugs are discovered and introduced all the time and their immediate requirement has to be met through imports until the know-how is available indigenously. The import of technology can be considered only in cases where the same is not available for immediate exploitation.

There are turbulent developments taking place in fine chemicals, and as a result, this sector is growing faster than ever before. New products and processes are emerging. The relationship between suppliers and the customers is changing. Some markets are undergoing globalization. Mergers and acquisitions are taking place, and this is consolidating the sector. It is still

too early to say that the fine chemical industry is maturing. However, its puberty is certainly over, and it has definitely entered its adolescence.

A lot of developments are taking place in fine chemicals, and many of these are specific to certain market segment. This makes it difficult to sketch a complete picture of what is happening. What is true for most sectors of the fine chemicals industry and indeed, for most industries, is also true for fine chemicals; no company can escape the necessity to reduce costs. Competition has intensified, and customers have become more demanding. But what makes the fine chemicals industry so special is its potential for innovation. Over the last 10 years, this sector has made tremendous progress and developed processes. The developments in the markets show a clear correlation with developments in technology and show the importance of innovation in fine chemicals.

INNOVATION IN FINE CHEMICALS

Despite the increased competition in generic segments, there is no reason for the fine chemicals industry to be pessimistic about its future. On the contrary, the industries have never been in such a good position. The prospects offered by technological developments are excellent.

The pharmaceutical industry, which uses around half of the fine chemicals produced in the world, is a very dynamic sector. Major companies have merged, others have been acquired, and as a result, innovation is picking up fast. For example, due to combinatorial chemistry, pharmaceutical companies are cutting the time it takes to come up with new and effective drugs. Add to this the steady growth of chiral drugs, and it is clear that over the next few years there will be numerous and improved drugs hitting the market.

More and more pharmaceutical companies are deciding to use the expertise of fine chemicals in order to make best use of process expertise to accelerate the market entry of new drugs. This is boosting the demand for fine chemicals intermediates and active ingredients. The challenge facing us is to exploit this trend to the fullest.

A combination of the market pull and technology push is giving a fresh boost to growth in fine chemicals. Whenever a pharmaceutical company contracts out its production, it is obviously taking a risk. Pharmaceutical companies prefer to contract out their production to producers who not only provide quality at an attractive price, but are also reliable. And clearly, major procedures prefer to deal with major suppliers having a wide range of technologies, who can, moreover, make the most of changing regulations².

ANXIOLYTIC AGENTS

Modifications of behavior, mood and emotion by drugs has always been a favourite indulgence of mankind³. Today, one out of every five prescriptions dispensed in the United States is for drugs intended to affect mental processes; to stimulate, sedate or otherwise modify feeling or behavior. The use of psychoactive drugs evolved along two related paths. Many of these efforts have led to the development of agents that are often classified into three major categories depending on their clinical usefulness:

- a) Neuroleptics,
- b) Antidepressants and mood stabilizers,
- c) Anxiolytics.

Anxiety:

Anxiety is not only a cardinal symptom of many psychiatric disorders, but also an almost inevitable component of many medical and surgical conditions. Indeed, it is a universal human emotion, closely allied with appropriate fear and often serving psychobiologically adaptive purpose.

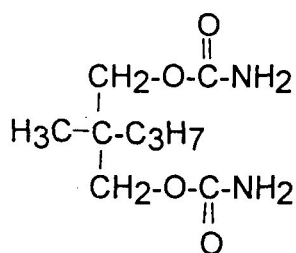
Symptoms of anxiety are commonly associated with neurotic depression, panic disorder, agoraphobia and other specific phobias and many personality disorders.

Anti-anxiety agents:

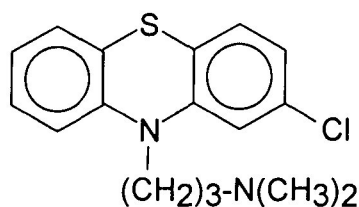
Barbiturates were the dominant anti-anxiety agents throughout the first half of this century⁵. However, by the 1950s, concern had arisen about their

propensity to induce tolerance, physical dependence and potential lethal reactions during withdrawal. This encouraged the search of the safer agents. Compounds such as, Meprobamate were the initial outcome. Despite the popularity of some of these agents for day time sedation or for hypnotic effects, an awareness developed that they shared many of the undesirable properties of barbiturates.

In 1954, Chlorpromazine the first synthetic drug, belonging to the class of phenothiazines (Antipsychotics) was reported by Laborit and co-workers⁴. Its use in psychiatric patients marked the beginning of modern psychopharmacology. The term 'tranquillizer' was introduced in the early 1950s by Yonkman to characterize the psychic effects of Reserpine. All the compounds discovered till early 1950s resembled barbiturates for their unwanted effects. This set the scene for the discovery of benzodiazepines in the late 1950s.



(I)
Meprobamate



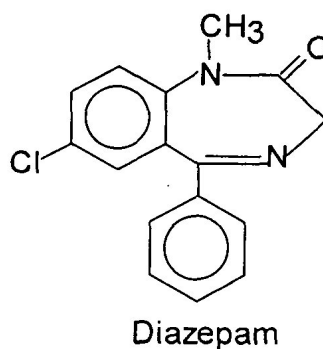
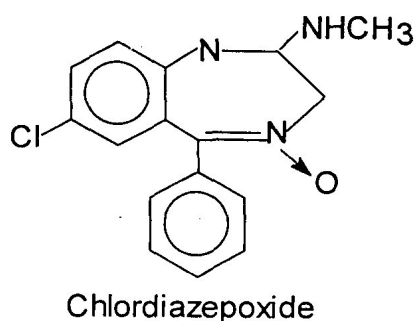
(II)
Chlorpromazine

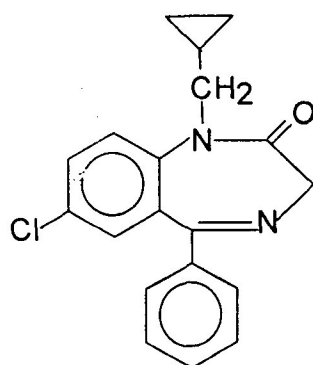
Discovery of 1,4-benzodiazepines as antianxiety agents:

The discovery of 1,4-benzodiazepines is an example of the serendipitous discovery of new drugs based on almost random screening of chemicals synthesized in the laboratory⁵. By the mid 1950s, psychopharmacology had developed to the point where the treatment of anxious patients with Meprobamate and psychotic patients with one of the aminoalkyl phenothiazine⁶ drugs was easily possible. There was a need for drugs of greater selectivity in the treatment of anxiety because of the side effects encountered with phenothiazines⁷.

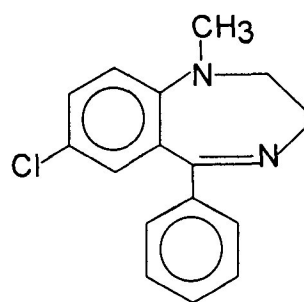
Thus, Sternbach a chemist⁸ decided to reinvestigate a relatively unexplored class of compounds, which he had studied in the 1930s. During synthetic studies he obtained compounds which he thought belonged to the class of 4,5 - benzo- (hept- 1,2,6-oxadiazines) or 1,3,4- benzoxadiazepines. Reinvestigations of these compounds revealed that they did not contain a 7-membered oxadiazine ring but were quinazoline-3-oxides. After 2 years, in 1957, the pharmacological testing revealed that it was not a quinazoline-3-oxide, but the result of unexpected reaction caused by primary amine used in synthesis. On treatment with methylamine, 6-chloro-2-chloromethyl-4-phenyl quinazoline-3-oxide did not furnish the expected 2-(N-methylaminomethyl) derivative, but instead, rearranged to 7-chloro-(N-methylamino)-5-phenyl-1,4-benzodiazepine-4-oxide. Shortly thereafter, Randall⁹ reported that this compound was hypnotic, sedative, with effects similar to that of Meprobamate (I). The compound was given the name Chlordiazepoxide marketed as Librium¹⁰.

Structural modifications of 1,4-benzodiazepine derivatives were undertaken and a 5-10 times more potent compound was synthesized, marketed as Diazepam. Diazepam¹¹ was the first potent 1,4-benzodiazepine derivative that did not contain a basic amino group, which was the original basis for the synthesis of these two compounds. Synthesis of many other experimental analogs soon followed and by 1983, about 35 benzodiazepines were available for their general sedative hypnotic and muscle-relaxant effects. Many of them were having selective anxiolytic¹² property, such as, Prazepam, Medazepam, Oxazepam, Lorazepam, Clorazepate, Bromazepam, Clobazam and Alprazolam, etc.





Prazepam



Medazepam

The various 1,4-benzodiazepines differ in their selectivity, pharmacological profile and clinical usefulness. They do not induce a true "anaesthetic effect", showed by the presence of awareness as well as muscular relaxation even after large doses¹³. True surgical anaesthesia results only after combining these 1,4-benzodiazepines with other central nervous system depressing agents.

1,4-benzodiazepines are the drugs of choice in the pharmacotherapy^{4,6} of anxiety and related emotional disorders, in the treatment of sleep disorders, status epilepticus and other convulsive states, as muscle-relaxants, for premedication and as inducing agents in anaesthesiology.

Mechanism of action of 1,4-benzodiazepines

Efforts to elucidate the mechanism of their action have met with good results. In 1974, sufficient evidence from behavioural, electrophysiological and biochemical experiments was accumulated to indicate that benzodiazepines act quiet specifically at synapse where gamma-amino butyric acid (GABA) is a neurotransmitter.

GABA is major inhibitory neurotransmitter in the mammalian CNS. Benzodiazepine receptors in the GABA ergic synapse have been localized by autoradiography and by using tissue-binding studies with radiolabelled agents⁴; leading to identification of specific, saturable, low-capacity, high affinity binding sites for tritiated diazepam or its analogs, such as, Flunitrazepam, in homogenates of mammalian brain tissue. The studies led to

increasing interest in benzodiazepine receptors. 1,4-benzodiazepines are found to potentiate GABA-mediated inhibitory neurotransmission and antagonize seizures caused by GABA depletion. *In vitro* binding studies support a GABA-benzodiazepine interaction¹⁴. GABA stimulates tritiated (³H) diazepam binding to synaptosomal membranes. The neurophysiological and biochemical evidences indicate that a GABA –benzodiazepine-chloride ionophore¹⁵ comprises a supramolecular structure. Therefore, an interaction between a 1,4-benzodiazepine and its receptors stimulates GABA receptors, activates chloride channel and increases inhibition.

The GABA-ergic synapse as primary site of action of 1,4-benzodiazepines:

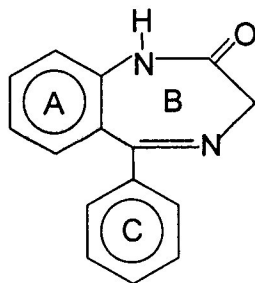
The benzodiazepines, in general, have been found to affect virtually all known neurotransmitters in CNS, at least in high doses. The proposal made by Haefly and Costa that benzodiazepines may produce their effects primarily by enhancing GABA-ergic transmission, provided an explanation for various secondary alterations induced by these drugs in other transmitter systems. The GABA acts on at least two different types of receptor types. The actions of benzodiazepines seem to be restricted to synaptic effects of GABA which are mediated by the so-called GABA receptors. The stimulation of these receptors by GABA results in an increase in the permeability of neuronal membrane by anions, mainly chloride ions¹⁴.

The 1,4-benzodiazepines mainly cause two effects:

1. They produce taming effect¹⁶ with decrease in aggressive behaviour in animals, in doses which do not decrease locomotor activity.
2. They act on spinal cord to depress polysynaptic reflexes.

Their locomotor or cellular sites of actions have not been elucidated, but they are thought to act relatively specifically to depress the limbic system and thereby reduce manifestations of emotions arising from connections between the limbic system and hypothalamus.

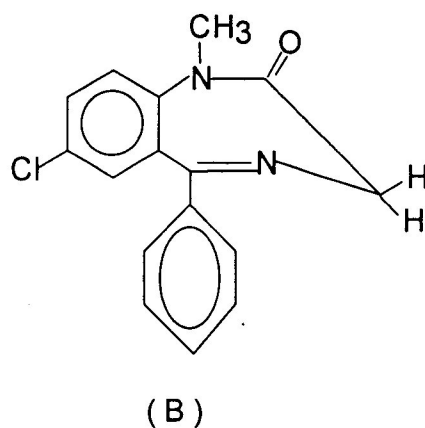
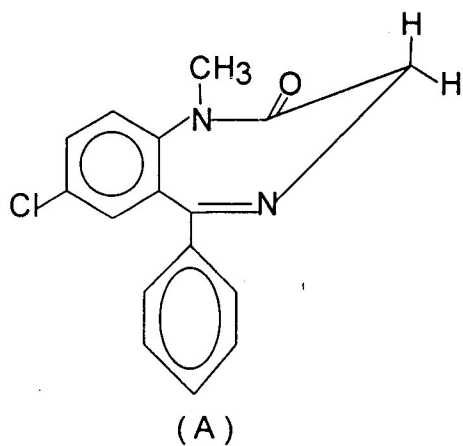
Chemistry and structure-activity relationship



Sternbach and collaborators¹⁷ recognised that the presence of 7-membered imino-lactum ring (B) was essential and the substitution in positions 1,2,3 and 7 is advantageous. Electronegative substitution, particularly in 7 and 2 position, increases activity.

Stereochemical consideration

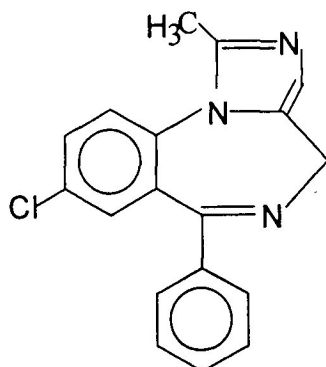
Most of the benzodiazepines have no chiral center; however their 7-membered ring (B) may adopt one of the two possible, energetically preferred boat conformations, i.e. (A) and (B) which are enantiomeric to each other.



At room temperature, the two conformations easily inter-convert. It is, therefore, impossible to predict which of the two will bind best to the receptor site. The *in-vivo* and *in-vitro* activities are found to be restricted to the enantiomers possessing the S-configuration.

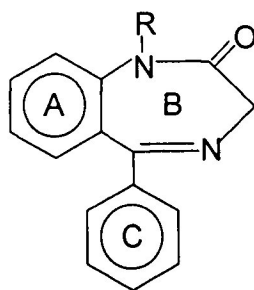
The 3-methyl group results in stabilization of conformation (A) for ring (B) of the S-enantiomer and is located in the pseudo-equatorial position. Thus, conformation of ring (B) is determinant for the affinity for the benzodiazepine receptor.

Condensation of an additional ring on the 1,2-band of the 1,4-benzodiazepine nucleus resulted in interesting compounds. Thus, s-triazolo-benzodiazepines were discovered.



Alprazolam

Effects of substituents on the biological activity of benzodiazepines



The substitution at 7 position of the ring by :

Ring A : Electron withdrawing¹⁸ substituents, e.g. halogens, -NO₂, -CF₃, etc. increase activity whereas electron donating groups, such as -CH₃ and -OCH₃ decrease activity.

Ring B : N'-methyl substitution increases whereas larger groups decrease activity.

Ring C : Halogen substitution at 2' position increases activity, whereas that at 4' position decreases activity strongly.

Therapeutically useful 1,4-benzodiazepines are markedly lipophilic and their log P values lie between 1.44 and 4.44. On biotransformation, *In-vivo* and *In-vitro*, they give centrally active metabolites.

1,4-benzodiazepines are very widely used, since they are efficacious, safe and fatal overdose is extremely uncommon. They are used not only for the treatment of anxiety neurosis, but also to allay the ordinary stresses and tensions of every day life.

HISTAMINE H-1 ANTAGONISTS

When a previously sensitized individual produces an adverse response to a foreign chemical or to a physical condition, that individual is said to have an allergy. Such hypersensitivity reactions cause many chronic and acute illnesses, including hay fever, pruritis, contact dermatitis, drug rashes, urticaria, atopic dermatitis, and anaphylactic shock.

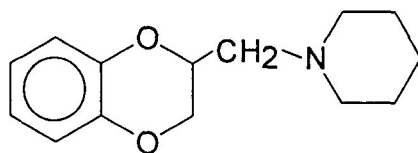
An immediate (anaphylactic type) allergenic reaction may develop in seconds when a presensitized individual comes in contact with an allergen. Anaphylaxis is an intense, systemic allergic reaction that, in some cases, is fatal. In delayed allergies, the reaction is mediated by cells (i.e. lymphocytes), and symptoms may take up to 24 hrs to appear. In this case, a reaction does not occur between an antigen and a circulating antibody. Whether or not an allergic reaction is of the immediate or a delayed type, the precipitating factor involves interaction of two macromolecules, an antigen (immunogen) and an antibody.

As part of the allergic responses to an antigen, antibodies (Ig E) are generated, and these bind to the surface of the mast cells and basophils. The Ig E molecule functions as a receptor and interacts with a signal transduction system in the membranes of sensitized cells¹⁹. On subsequent exposure, the antigen bridges the Ig E molecules and causes activation of Phospholipase C. This action leads to the generation of inositol-1,4,5 tris(dihydrogen phosphate), diacylglycerol and causes an elevation of intracellular calcium²⁰, which triggers off the release of secretory granule contents by exocytosis.

Dale and Laidlaw first suggested that histamine was the mediator associated with allergic manifestations^{21,22}. This substance is still accepted as the cause

of Wheal and Flare response in the skin and is thought to play a major role in producing the symptoms of allergic rhinitis. These pharmacologic effects of histamine and structurally related compounds are referred to as the actions of the agonist. Antiallergic agents that block some of the actions of histamine are known as anti-histamine or more specifically, as histamine H-1 antagonist. Structural requirements for histamine (agonist) activity are different from those required for antagonist activity.

By the beginning of the 20th century, the imidazole ring was known to occur in the amino acid histidine, the alkaloid pilocarpine and histamine, all of interest to the biologically oriented chemists at that time. Its synthesis was accomplished in 1907. The vascular effects of this biogenic amine were not fully recognized for another decade, neither was its wide occurrence and distribution in animal tissues. In 1920, the histamine-stimulated secretion of gastric acid was demonstrated. However, it was Best *et al.* (1927) who identified histamine in high concentrations in the lungs. They observed that it causes vasoconstriction, respiratory distress, and shock like syndrome following intravenous administration in animals. Later the role of histamines in the pathogenesis of the anaphylactic reaction was established. An association of histamine with asthma (intravenous histamine in asthmatic patients decreased vital capacity and caused a parallel release of histamine with bronchoconstriction) briefly led to false hope that antihistamines might be useful in treating chronic asthma. There is a possibility that the limitations of dosage imposed by the adverse effects of the earlier classic antihistamines simply did not supply enough drug effectively to antagonize the copious amounts of histamine released during asthma attacks. Now, with newer, more potent and less toxic compounds on the horizon, the hypothesis may again be open to verification.

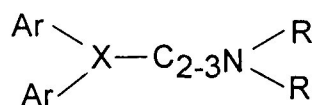


929 F

The basic piperidinomethylbenzodioxide (929 F), is considered as the first compound shown to have antihistaminic properties *In-vivo*, since it protected animals from the bronchial spasms induced by exposing them to histamine vapours (Fourneau and Bovet, 1933). The anticholinergic effects of this compound can be rationalized by viewing it as a basic choline ether. This property, became an annoying side effect of almost all the antihistamines introduced over the next several decades.

Drugs developed during the 1940s (e.g., Pyrilamine and Diphenhydramine) were marketed for the treatment of various allergic conditions such as urticaria and hay fever, for which they are still in use. Many additional drugs joined these two pioneering agents. Ultimately, five chemical classes of histamines evolved :

1. Ethanolamine derivatives
2. Ethylenediamines
3. Alkylamines
4. Piperazines
5. Phenothiazines and other Polycyclics.



Almost all the classic antihistamines can be summarized into a general structure of a diaryl system with a 2-(or3-) carbon aminoalkyl side chain.

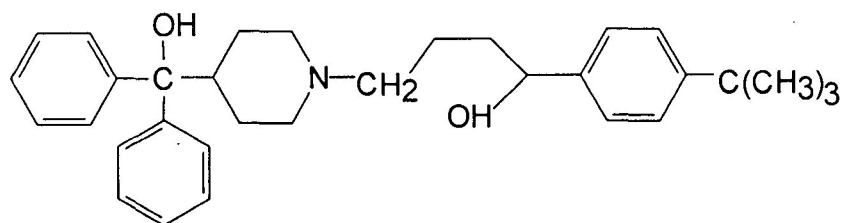
The concept of isosteric replacement within organic compounds to improve or otherwise modify their biologic effects that were introduced in the early 1930s, was first successfully applied to antihistamines and to antibacterial sulfonamides. It proved to be an extremely useful early tool in what may retrospectively be called rudimentary drug design. For example, by exchanging the oxygen atom in the ethanolamine aryls like diphenhydramine or other type of antihistamines with one nitrogen, one obtains an equivalent, or possibly superior, histamine antagonist of the ethylenediamine type, as well

as achieves a degree of differentiation of antihistaminic activity from the considerable anticholinergic effects of the former agent.

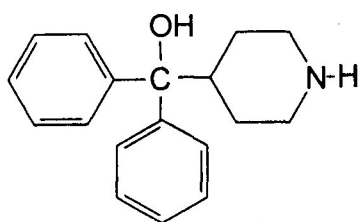
H-1 antagonist with decreased sedative properties:

The major side effect of the classic H-1 antagonists is possibly attributable to occupation of cerebral H-1 receptors²³. Central nervous system effects are to be anticipated because most classic antihistamines cross the blood-brain barrier. During the 1980s, H-1 receptor antagonists with better clinical properties were discovered. These substances have a relatively low affinity for central H-1 receptors, a limited ability to penetrate the CNS, or both. Consequently they are largely free of side effects, especially sedation.

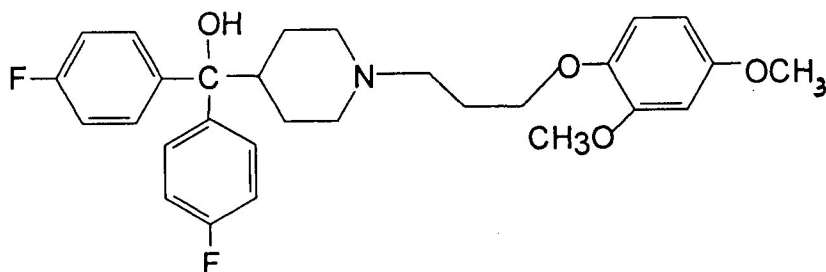
A particularly interesting modification of cyclic basic chain of a Cyclazine analog led to the development of Terfenadine (U.S.P.), an H-1 antagonist with virtually no side effects²⁴ such as dizziness, drowsiness, and fatigue, which are common with classic antihistamines²⁵. In contrast, the sedative effect of one early antihistamine, Promethazine, is so intense that a suggestion was made to use it as an antipsychotic agent²⁵. The relationship between Promethazine, the N-methyl derivative of the antihallucinatory agent Azacyclonol, and the general structures of H-1 antagonists led to studies of the properties of Azacyclonol derivatives. Modification of this structure produced fluorobutyrophenones related to Haloperidol, which has weak antipsychotic activity with potent H-1 antagonist properties²⁴.



Terfenadine

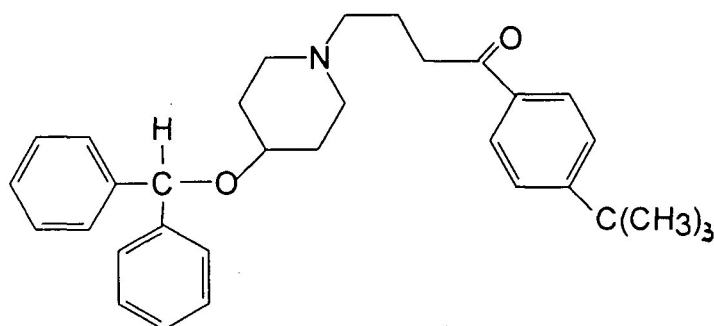


Azacyclonol



AHR-533B

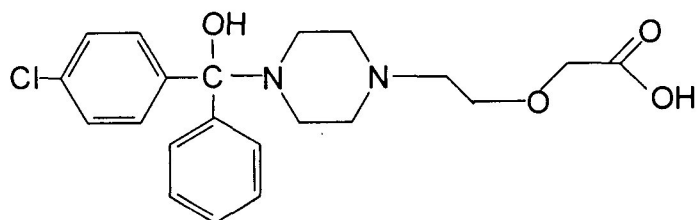
Replacement of the fluorine atom by t-butyl group and reduction of the ketone to an alcohol resulted in the H-1 antagonist, Terfenadine. This non sedating compound has enjoyed popularity in the treatment of allergic manifestations. In a series of 4-(diarylhydroxymethyl)-1-[3-(aryloxy)-propyl] piperidines, the 4-fluorophenyl derivative, AHR-5333B, is more effective than Terfenadine²⁶ and has undergone clinical investigations.



Ebastine

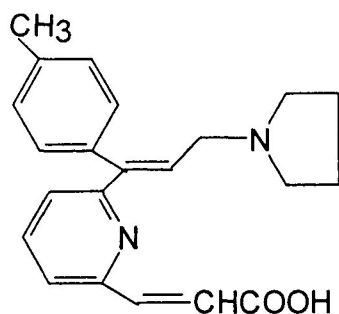
Ebastine, commercialized in 1990 in Spain, may be viewed as a structural hybrid of Diphenylpyraline, a potent classic H-1 antagonist, and Terfenadine. As such, it combines potent, long lasting, and selective blockade of histamine H-1 receptors with an absence of sedative effects, and like Ternaftidine, undergoes biotransformation to active carboxylic acid metabolites by oxidation of one methyl group of the t-butyl moiety. Whereas the acid metabolite of

Ternaftidine is less potent than its precursor as an H-1 antagonist, the equivalent metabolite derived from Ebastine has been found to possess considerably more anti-histaminic activity *In-vivo*.



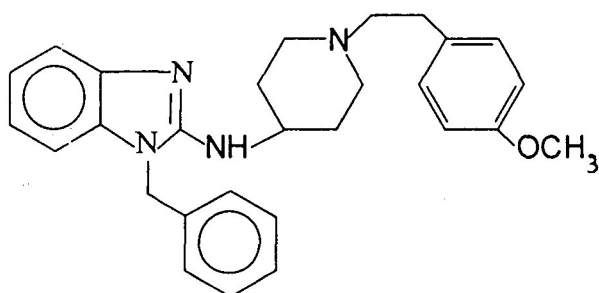
Cetrizine

Cetrizine is the main metabolite of Hydroxyzine because of its higher polarity. This Zwitter ionic compound less readily penetrates the blood-brain barrier than does the parent compound. Accordingly, this drug also has reduced sedative side effects.



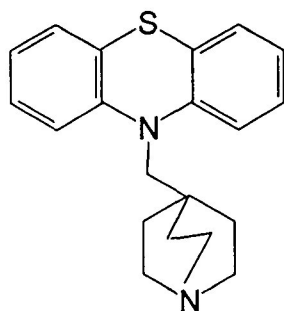
Acravastine

Acravastine is derived from the classic antihistamine Triprolidine by insertion of a carboxyethynel function at the 2-position of the pyridine ring. This peripheral H-1 receptor antagonist has activity similar to that of Triprolidine. Animal tests show that this Zwitter ionic compound only slowly passes the blood-brain barrier and is less sedative than the parent drug.



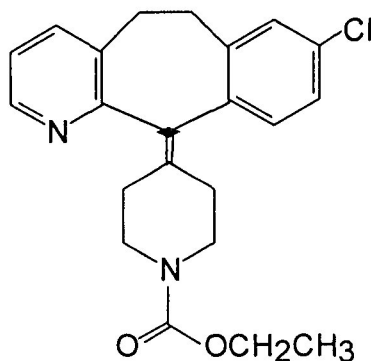
Astemizole

Astemizole, a non-sedative anti-histamine, structurally resembling Clemizole and developed during the investigations of 2-amino benzimidazole, is a potent H-1 receptor antagonist with a long duration of action. This drug has no anticholinergic or local anesthetic properties. Astemizole is metabolised slowly and extensively, mainly by aromatic hydroxylation and oxidative dealkylation. The desmethyl metabolites are pharmacologically active and are likely to contribute to the extended duration of anti-histaminic action. From the studies *In-vitro* and *In-vivo*, it appears that the reduced level of CNS activity of Astemizole is related to its poor penetration of the blood-brain barrier.



Mequitazine

Mequitazine is a tricyclic analog in which the basic side chain is positioned within a quinuclidinyl methyl substituent. This drug has less sedative effect than Promethazine.



Loratidine

Loratidine is a hydrophobic analog of Azatidine, obtained by addition of an aryl chloro group and derivitization of the otherwise basic piperidino nitrogen as the neutral carbamate. H-1 antagonist potency is comparable to that of Ternaftidine. The drug has a long duration of action and little or no CNS side effects.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

These drugs may be defined as "classic" nonsteroidal anti-inflammatory agents because they are active in the carrageenan induced edema, adjuvant arthritis, ultraviolet-erythema assays, and as antipyretics.

Inflammation, however, is a normal, essential, protective response to noxious stimulus that may threaten the host and may vary from the localized reaction to a complex response involving the whole organism.

Anti-inflammatory drugs modify inflammatory responses to diseases, but are not curative and do not remove the underlying cause of the disease. An ideal anti-inflammatory drug should affect only aberrant, uncontrolled inflammation response, which is a part of the body's vital defence mechanism to invading microorganisms and other environmental insults.

In the past 25 years, intensive research has been aimed towards discovering nonsteroidal anti-inflammatory drugs with the therapeutic effectiveness of the glucocorticoids, but without their undesirable side effects. About 30 nonsteroidal anti-inflammatory drugs (NSAIDs) have been marketed in the United States and England. The drugs that have been introduced seem to have substantial sales. Data suggest that introduction of a new NSAID is not associated with a corresponding reduction in the prescribing of the other NSAIDs²⁷. Nearly every drug firm in the United States is trying to capture a share of the large and expanding market for drugs to treat rheumatoid arthritis and related disorders.

Although improved therapy is still desperately needed for rheumatic arthritis and osteoarthritis, beneficial drugs are available. These products relieve pain, swelling, and inflammation and enable many patients with mild to moderate rheumatic disease to lead essentially normal lives. They include drugs such as Aspirin and the Salicylates, Indomethacin, Sulindac, Ibuprofen, Fenoprofen, Naproxen, Tolmentin, Penicillamine, Meclofenamic acid, and the Gold compounds.

The sequence of events of carrageenan-induced edema of the rat paw has been delineated. The action of the initial edema mediators, histamine and serotonin, is succeeded by a second phase in which increased vascular permeability is maintained by kinin release. This is followed by a third phase, prostaglandin release, which starts the migration of leukocytes into the site of inflammation. Nonsteroidal anti-inflammatory agents suppress this migration. Activation and release of all the foregoing mediators depend on an intact complement system. For comparison, Indomethacin and Phenylbutazone are 148 and 3.3 times, respectively, as potent as Aspirin in producing 50% inhibition of carrageenan-induced rat paw edema²⁸.

Because the clinically useful nonsteroidal anti-inflammatory drugs differ widely in chemical and physical properties, attempts have been made to compare the biochemical properties of these compounds to determine possible modes of action. These drugs are polyvalent and are able to modulate more than one molecular or cellular event thought to be concerned in the inflammatory event.

Nonsteroidal anti-inflammatory drugs have many biochemical activities²⁹. They are said to inhibit formation of the inflammatory mediators (Histamine, Serotonin, Prostaglandins, and kinins) and to moderate the activity of the inflammatory processes. They are also believed to inhibit oxidative phosphorylation, which deprives the inflamed tissue of needed metabolic energy in the form of adenosine triphosphate(ATP). They may displace anti-inflammatory peptides from albumins, or they may hyperpolarise neuronal membranes, especially in the acidic environment of the inflamed tissue. The drugs are also believed to stabilize lysosomal membranes.

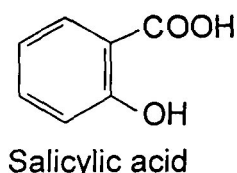
The development of anti-inflammatory drugs started with the use of salicylates at the end of the 19th century. Interest in pyrazolones during the 1940s resulted in the discovery of the activity of Phenylbutazones. The 1950s brought the corticosteroids. Then came an effort to find potent nonsteroidal substances, without the side effects of the corticosteroids (e.g. osteoporosis, ulcerogenicity, and salt retention), which culminated in the 1960s with

Indomethacin and other arylacetic acid derivatives. In the 1970s, a new generation of aryl acids was available.

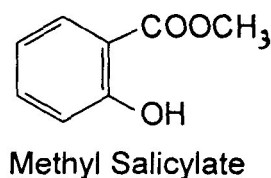
The clinically useful nonsteroidal anti-inflammatory drugs have diverse chemical structures, but they also have some similar features as well as common biochemical properties.

Salicylic Acid Derivatives :

The drugs most widely used to treat arthritis are derivatives of salicylic acid.



In 1928, Leroux isolated the glycoside salicin from willow bark (*Salix alba*) used since antiquity as an antipyretic. On hydrolysis, salicin produces glucose and salicyl alcohol (saligenin). In 1838, Piria made salicylic acid from salicin, and in 1844, Cahours prepared it from oil of wintergreen (methyl salicylate).



The major chemical classes of salicylates used in medicine are the esters, salts, and amides of salicylic acid obtained by substitution at the carboxyl group, and the salicylate esters of organic acids that are obtained by substitution at the phenolic OH group and that having an intact carboxyl group.

Absorption, Distribution, Metabolism and Excretion :

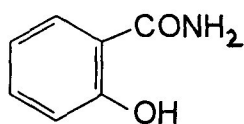
The salicylates have been the drugs most widely used to treat inflammatory and rheumatic diseases ever since this clinical activity was discovered in 1875. Many theories have been proposed for the mechanism by which the salicylates produce their inflammatory effects. A complicating feature has been that Aspirin and the salicylates, along with the Aspirin-like nonsteroidal

anti-inflammatory agents such as Phenoxybutazone, Mefenamic acid, Indomethacin, Tolmentin, Ibuprofen, Fenoprofen, and Naproxen, have been active in almost every biologic system in which they have been tested. Because inflammation is a complex process that can be induced by various means and can be mediated by a number of only partly known mechanisms with multiple manifestations, it would not be surprising if anti-inflammatory agents exert their effects through a spectrum of different biochemical modes of action.

Some of the possible mechanisms for the anti-inflammatory actions of Aspirin like drugs include antagonism of kinin actions and prostaglandin biosynthesis prevention of leukocyte accumulation; inhibition of mucopolysaccharide and glycoprotein biosynthesis resulting from decreased availability of energy in the form of ATP and inhibition of enzymes involved in the synthesis of these macromolecules, increased collagen turnover with repair of connective tissues, and prevention of release of lysosomal enzymes through stabilization of the lysosomal membrane³⁰.

Salicylamide :

This drug, o-hydroxybenzamide, has been suggested as an effective substitute for Aspirin in rheumatic disease.



Salicylamide

It is stable in liquid preparations, does not cause gastrointestinal ulceration, and can be taken up by person allergic to Aspirin.

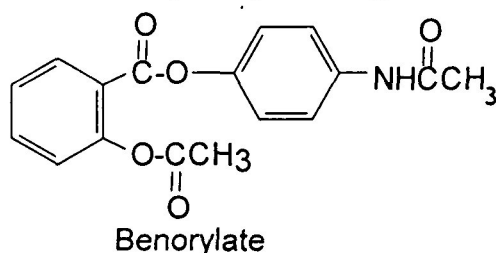
Salicylamide has been reported to be an effective analgesic for pain associated with rheumatic disease when administered in doses of at least 6g. Other investigators, however, have been unable to find any anti-rheumatic activity clinically under double blind conditions, and have concluded that salicylamides has no useful anti-inflammatory or anti-rheumatic activity³¹.

Because salicylamide is not hydrolyzed to salicylate, its analgesic activity depends on the entire molecule.

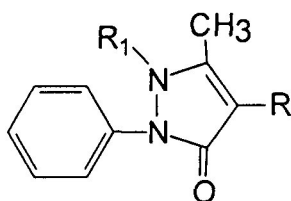
Derivatives of aniline and p-aminophenol, as exemplified by Acetaminophen, have analgesic activity similar to that of Aspirin but lack anti-inflammatory and anti-rheumatic activity. Preparations containing combinations of salicylamides and Acetaminophen therefore seem to have little use in the treatment of rheumatic disease.

Benorylate :

Benorylate (Benoral), marketed in Europe as an anti-inflammatory drug, is an ester of acetylsalicylic acid with acetaminophen. The *in-vivo* hydrolysis gives two compounds with complementary activity in different drug classes. Benorylate is reported to cause less gastrointestinal bleeding than Aspirin³². Acetaminophen nephrotoxicity, however, is reported to be enhanced by concurrent Aspirin administration³³. Studies of Benorylate in the U.S.A. were halted when test animals developed eye damage.



5- Pyrazolone Derivatives :



Antipyrine (Phenazone) $R_1 = \text{CH}_3$, $R_2 = \text{H}$.

Aminopyrine (Amidopyrine) $R_1 = \text{CH}_3$, $R_2 = \text{N}(\text{CH}_3)_2$.

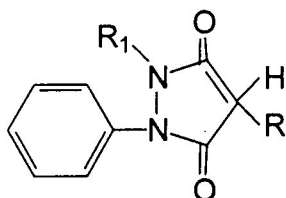
Dipyrone (methampyrone), Narone, and pyrilgin $R_1 = \text{CH}_3$,

$R_2 = \text{H}_3\text{CNCH}_2\text{SO}_3\text{Na}$.

Antipyrine and Aminopyrine have analgesic, antipyretic, and anti-rheumatic activities similar to those of Aspirin and sodium salicylate, and were formerly widely used for the same purposes. Fatal agranulocytosis caused by their application (especially associated with dipyrone and aminopyrine) led to a curtailed use of these drugs.

3,5-Pyrazolidinedione Derivatives :

The 5-Pyrazolones are important because they led to the potent phenylbutazone class of anti-inflammatory agents.



Phenylbutazone (Butazolidin) $R_1 = C_6H_5$; $R_2 = n-C_4H_9$.

Oxphenbutazone (Tanderial) $R_1 = p-HOC_6H_4$; $R_2 = n-C_4H_9$.

Sulfinpyrazone (Anturane) $R_1 = C_6H_5$; $R_2 = CH_2CH_2SOC_6H_5$.

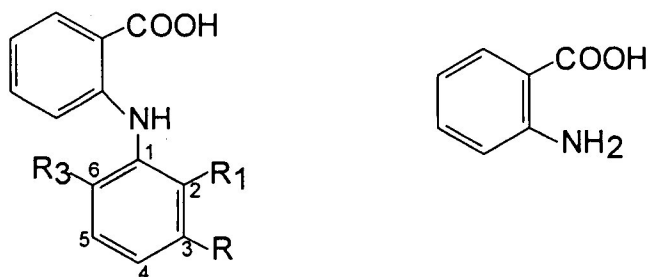
Phenylbutazone has analgesic and antipyretic properties but shows no advantages over Antipyrine and Aminopyrine. The sodium salt of Phenylbutazone, however, was found to solubilise several sparingly soluble drugs, including Aminopyrine. Phenylbutazone competes for the same binding sites on human plasma albumin as coumarin anticoagulants, sulfonamides, Tolbutamide, Indomethacin, glucocorticoids. This competition and displacement of the drug from the binding sites may result in increased pharmacologic activity and toxicity.

Mode of Action :

Phenylbutazone plays a diverse biochemical reactions, similar to those listed earlier for the nonsteroidal anti-inflammatory agents. Some of the biochemical modes of action proposed for Aspirin may also apply to Phenylbutazone. These include uncoupling of oxidative phosphorylation, inhibition of prostaglandin synthesis, inhibition of the histamine forming enzyme histidine decarboxylase, stabilization of lysosomal membranes, and inhibition of mucopolysaccharide biosynthesis.

N-Arylanthranilic Acid (Fenamates) :

Derivatives of anthranilic acid, such as Mefenamic acid, Meclofenamic acid, and Flufenamic acid, are potent analgesic and anti-inflammatory agents. These fenamates are nitrogen analogues of Salicylic acid; Anthranilic acid is also an o-substituted benzoic acid.



Mefenamic acid, introduced in the United States in 1967 has been approved by the Food and Drug Administration only for use in the management of pain and treatment of primary dysmenorrhoea. Meclofenamic acid, as the sodium salt (generic name Meclofenamate Sodium), was released in the United States in 1980 for the treatment of rheumatoid arthritis and osteoarthritis. Flufenamic acid is marketed in Great Britain for the treatment of rheumatic disease.

In clinical studies, phenylbutazone was approximately twice as potent as Flufenamic acid and 5 times as active as mefenamic acid in arthritic patients.

Mefenamic acid is absorbed relatively slowly, mainly from the small intestine, and reaches maximal blood levels in 2 to 4 hours.

The mechanisms of anti-inflammatory and analgesic activity are probably similar to those of the other acidic nonsteroidal anti-inflammatory agents.

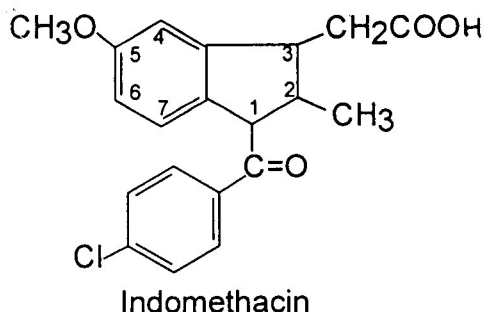
Mefenamic acid is indicated for the relief of mild to moderate pain, especially that following dental extraction.

Aryl and Heteroarylacetic Acid Derivatives :

These are important nonsteroidal anti-inflammatory agents making up large part of the nonsteroidal anti-inflammatory prescription market. These drugs may be classified according to the aryl or heteroaryl moiety.

Indomethacin was introduced in the United States in 1965 and is one of the most potent nonsteroidal anti-inflammatory agents.

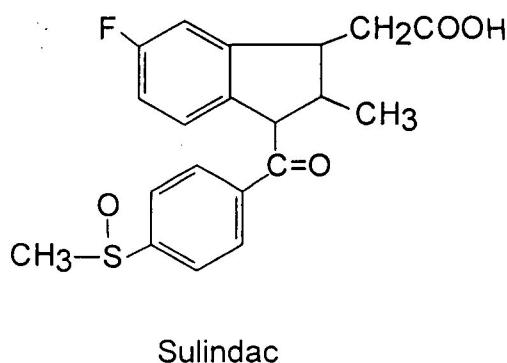
Indomethacin is rapidly absorbed and excreted, with peak blood levels being reached within 2 hours after oral administration.



The mode of action may be polyvalent and similar to that of the other acidic anti-inflammatory agents, such as Aspirin, Phenylbutazone, and Mefenamic acid. The anti-inflammatory effects of Indomethacin are not a result of stimulation of the production or release of corticosteroids.

Sulindac :

It is an anti-inflammatory agent marketed in the United States since 1978.



The heterocyclic nitrogen atom was removed from Indomethacin in an effort to lessen the central nervous system and gastric irritancy side effects of the

parent drug. The resultant indene isoster, cis-1-(p-chlorobenzylidenyl) indene 3-acetic acid (Sulindac), proved to be an active compound lacking central nervous system side-effects and causing less irritation to the gastrointestinal tract.

Sulindac is a "pro-drug"; its active form is the sulfide metabolite, which has a relatively long half-life, making possible a clinical schedule of twice-daily administration.

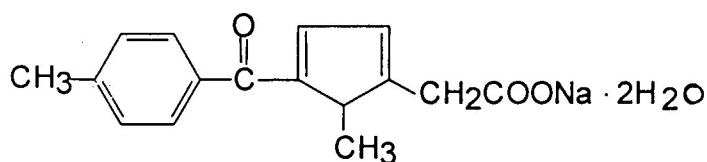
Pyrroleacetic Acid Derivatives :

Tolmetin, U.S.P.

Tolmetin (sodium salt) was introduced in the United States in 1976 as a new drug for the relief of inflammation and pain of rheumatoid arthritis.

Tolmetin sodium is rapidly absorbed and readily eliminated after oral administration, reaching peak plasma levels within 30 to 60 minutes, with half life of 60 minutes.

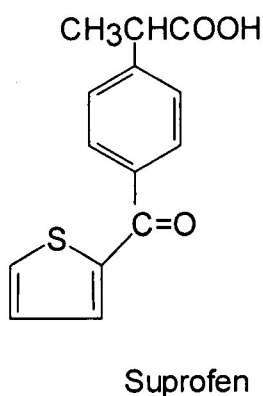
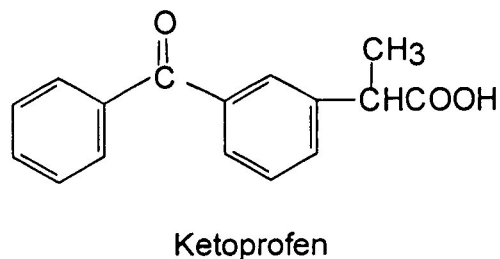
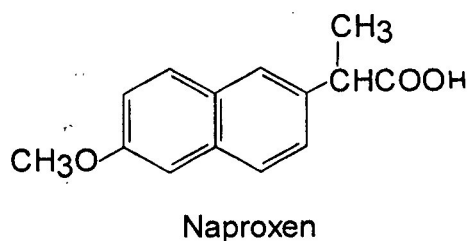
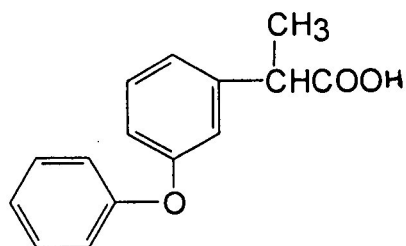
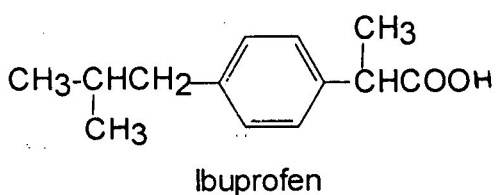
Tolmetin Sodium inhibits prostaglandin formation by inhibiting prostaglandin synthetase. This may be the primary mechanism of anti-inflammatory activity. Tolmetin Sodium also inhibits polymorph migration, has antipyretic activity, and decreases capillary permeability.



Tolmetin sodium

Phenyl- α -Methylacetic Acid Derivatives :

Many phenyl- α -methylacetic acid derivatives have been presently synthesized and found to possess anti-inflammatory activity; four such agents presently commercially available in the United States are Ibuprofen, Fenoprofen, Ketoprofen, Suprofen and Naproxen.



Ibuprofen U.S.P. :

Ibuprofen is rapidly absorbed when administered orally, reaching peak blood levels in one hour, and decreasing to about one-half of peak in 4 hours.

The mode of action of Ibuprofen is similar to that of the other acidic nonsteroidal anti-inflammatory agents in being related to the inhibition of prostaglandin formation.

Fenopropfen is a typical lipid-soluble carboxylic acid and is rapidly absorbed on oral administration, achieving peak plasma levels within two hours, with a plasma half life of approximately 3 hours. Fenopropfen inhibits the collagen induced platelet aggregation, shows *In vitro* activation of the fibrinolytic system, stabilizes lysosomal membranes, and inhibits phagocytosis and complement functions.

It is rapidly and completely absorbed from the gastro-intestinal tract, giving in the plasma the unchanged compound, hydroxylated metabolites and their respective glucuronides.

Suprofen :

Suprofen is rapidly and completely absorbed from the gastrointestinal tract with peak serum levels occurring within one hour of oral administration.

Suprofen is approximately six times as potent as Retoprofen.

Napthalene Acetic acid derivatives :

Naproxen is an acidic, highly albumin-bound drug. After oral administration, it is promptly and fully absorbed. The mean half-life of the drug is 13 hours, close to ideal for twice daily administration.

Naproxen, like most other nonsteroidal anti-inflammatory agents, inhibits prostaglandin synthesis. This is the most probable mechanism of action.

A new class of nonsteroidal anti-inflammatory compounds that are not carboxylic acids is exemplified by the potent agent Piroxicam.

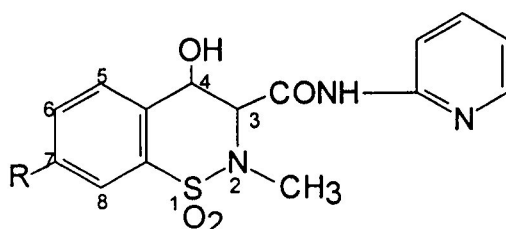
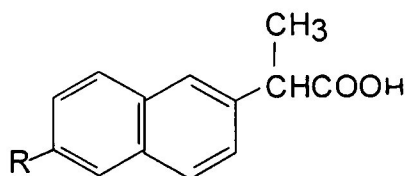
Piroxicam is well absorbed after oral administration with peak drug plasma concentrations reaching within 3 to 5 hours after administration.

Piroxicam is a potent inhibitor of prostaglandin biosynthesis through inhibition of the cyclooxygenase step of arachidonic acid metabolism, and thus may have a mechanism of activity similar to that of the other acidic non-steroidal anti-inflammatory drugs.

Topical Anti-Inflammatory Agents :

The use of these drugs may be extended to that of topical, nonsteroidal anti-inflammatory agents. The butyl ester of Flufenamic acid and the 2-pyridinemethanol ester of Ibuprofen have been marketed in Japan for the topical treatment of acute and chronic eczema and of contact and atopic

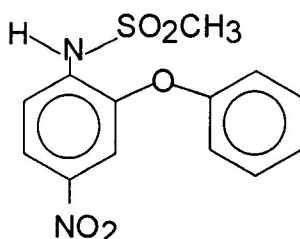
dermatitis, Piktetoprofen, an amide derivative of Ketoprofen, is available in Spain in aerosol form for topical treatment of inflammatory and painful musculoskeletal disorders.



Eicosanoids-Prostaglandins, Thromboxanes and Leukotrienes :

Considerable evidence has supported the role of prostaglandins as primary contributors to conditions of inflammation, pain and fever. It has provided the concept that non-steroidal anti-inflammatory drugs act by inhibiting the biosynthesis of prostaglandin³⁴. Prostaglandins are a group of cyclopentane derivatives formed from 20 carbon polyunsaturated fatty acids by most mammalian tissues, and they exhibit a variety of physiologic activities. The prostaglandins, due to their influence on biologic processes near their point of release and by possessing mechanisms for their inactivation at or near the locus of release, have therefore been referred to as "local hormones".

Sulphonanilides :



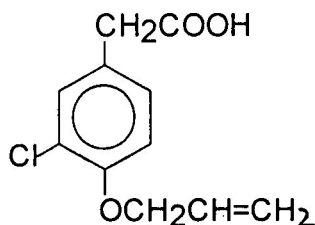
Nimesulide

Nimesulide, a sulfonamide, is a leading molecule, which has shown a significant inhibitory selectivity towards cyclooxygenase-2 without affecting cyclooxygenase-1. It is a new nonsteroidal anti-inflammatory agent given

orally or rectally on a twice a daily basis in a number of inflammatory and painful conditions.

Phenyl Acetic acid derivatives :

Ibuprofen was the first compound to be synthesized in this series. The newer analogues of phenylacetic acid derivatives have achieved more success than Ibuprofen.



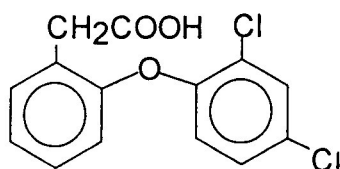
Alclofenac

Alclofenac is employed largely for the relief of muscular and rheumatic pain. While the incidence and severity of gastrointestinal side effects is perhaps less, the drug causes a severe rash with systemic manifestations in a high percentage of cases.



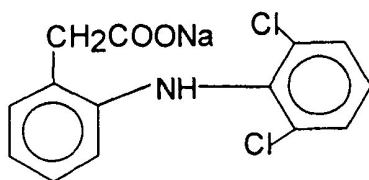
Bufexamac

Bufexamac is used in the form of a cream for the local treatment of pruritis, psoriasis and pain resulting from rheumatism and trauma.



Fenclofenac

Fenclofenac was used in the management of rheumatoid arthritis and osteoarthritis. It has been withdrawn from the market in the U.S.A. because of unacceptable level of adverse reactions.



Diclofenac Sodium

Diclofenac sodium is the most effective anti-inflammatory agent synthesized by Geigy researchers, after taking into account the structural and physicochemical characteristics of existing anti-inflammatory agents.

Plan of work

PLAN OF WORK

The discovery of any drug is followed by the appearance of several methods for its synthesis in the chemical literature. Different approaches to the drug synthesis are tried and obviously these utilize different drug intermediates. Despite the availability of several methods for synthesis of any particular drug, there is always a need for finding a more feasible and more economical method. The economy of this method, among many other factors, depends on the cost of drug intermediates used and their further processing. A viable drug project, from the economical and technological consideration, should take into account the following factors :

1. Availability of raw material.
2. Number of steps involved in synthesis.
3. Type of technology to be used for each synthetic step.
4. Type of chemical operations to be employed isolating products and recovery of raw materials solvent, useful by-products etc.

Some starting materials or intermediates may have toxic or adverse effects on the health of those processing them in bulk quantities. This problem could be solved by either doing away with such processes and substituting them with safer ones not involving hazardous chemicals, or taking all precautions during their handling and during exposure to their toxic vapours / fumes.

Many a times, the intermediates are not available indigenously for some reason or other and their demand has to be met by importing the chemical. This proves expensive in case of some drug intermediates. It becomes necessary to find out a suitable method for their synthesis and devise a feasible process that would make them available indigenously at a cost lower than that of the imported material. One of the main problems arising from the results of the work done is to utilize it effectively, so that some of the best efforts of the best brains of mankind are not wasted. Considering this point, economic studies were carried out and continually revived to obtain alternative processes. The synthesis of following drug intermediates was undertaken for the proposed work :

- 1) 2-amino 2'-fluoro 5-chlorobenzophenone.
- 2) 2-amino 2'-chloro 5-nitrobenzophenone.
- 3) 2-chloro 1-(4-fluorobenzyl) benzimidazole.
- 4) Intermediates for Aceclofenac.

It has been observed that these intermediates are in great demand because their availability is entirely met by importing them from abroad.

PART I and II :

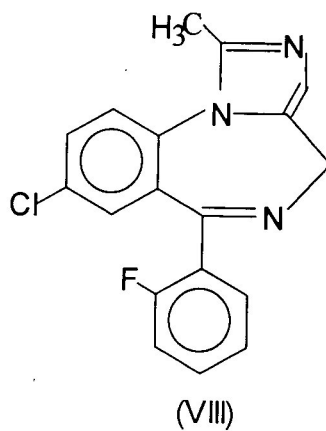
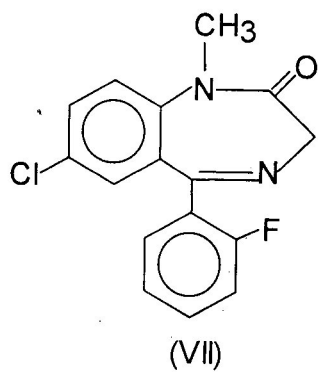
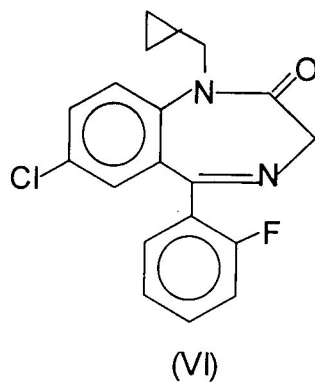
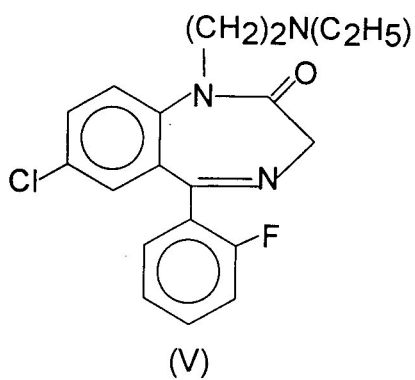
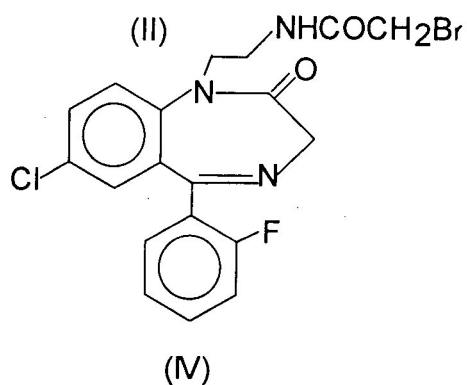
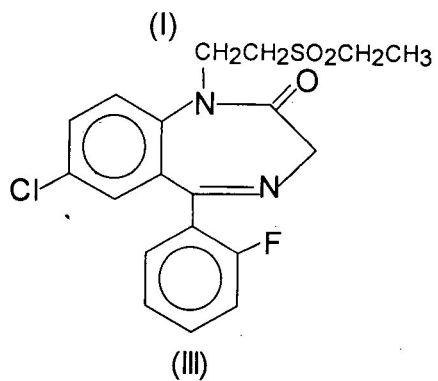
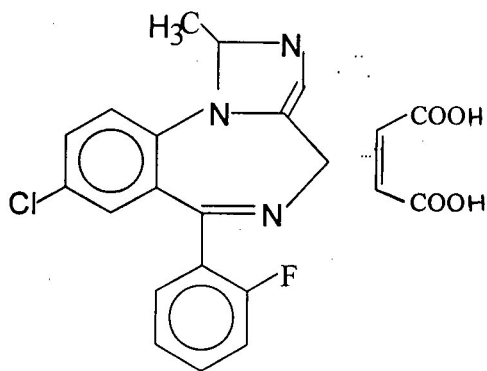
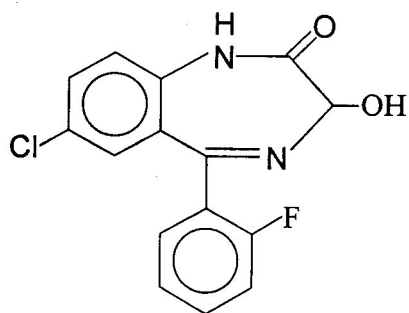
Advances in healthcare have dramatically increased life expectancy of human beings. Consequently, the incidence of many diseases associated with aging, including autoimmune, cardiac and metabolic diseases as well as those directly affecting central and peripheral nervous system, has increased. Diseases of the elderly are associated with anxiety and depression. Improved agents for treatment of these disorders and various dementias as well as therapeutic agents to improve, limit or reverse the neurodegenerative processes represents major challenges in CNS-related drug research. Indeed, statistical data in U.S.A. showed that one in four people may anticipate progressive impairment of cognitive functions³⁶. Anxiety is treated by benzodiazepines. While effective, benzodiazepines are sedative and muscle relaxants³⁷. Now a days there are about two dozen benzodiazepines in clinical use. A number of reviews have appeared which cover emerging therapies as well as clinical performances of more advanced candidates like Cinolazepam(I) and Midazolam maleate(II)³⁸⁻³⁹. Other drugs of importance which are in clinical use are : Eflazepam(III), Kenazepin(IV), Flurazepam(V), Flutoprazepam(VI), Fludiazepam(VII), Midolazepam(VIII), Quazepam(IX), Oxoqueazepam(X) and Doxefazepam(XI).

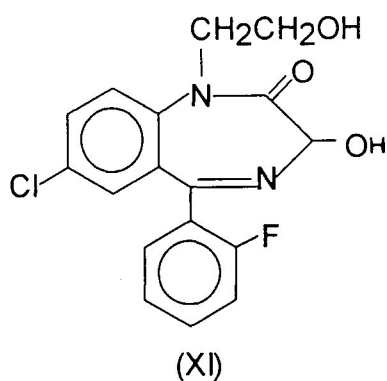
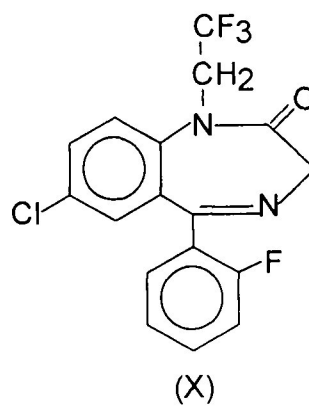
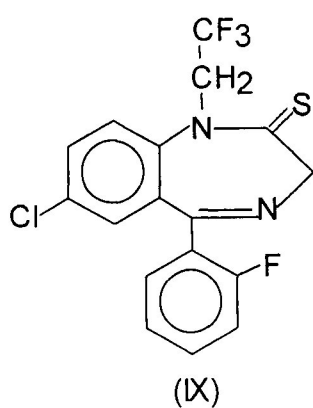
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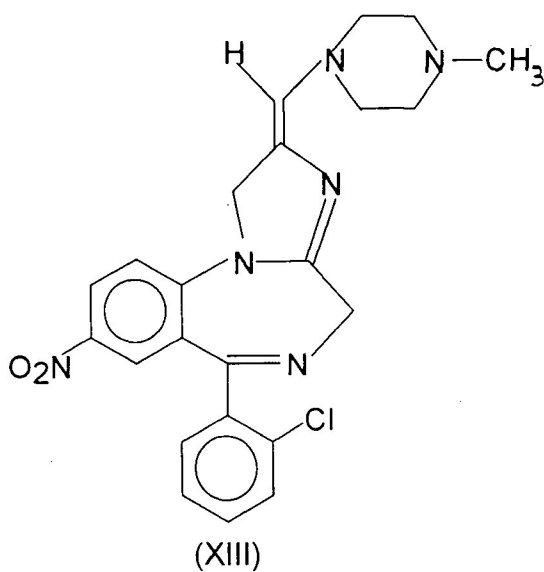
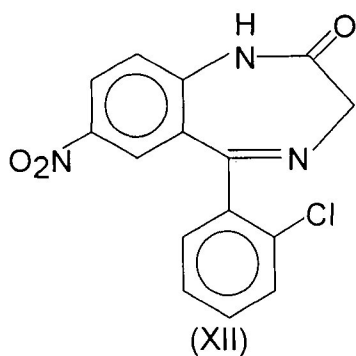
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All these drugs are synthesized from a common raw material, i.e. 2-amino 2'-fluoro 5-chlorobenzophenone.

Other drugs which are also used in clinical practice are : Clonazepam(XII) and Loprazolam(XIII). Synthesis of these drugs start from the raw material, 2-amino-2'-chloro 5-nitrobenzophenone.

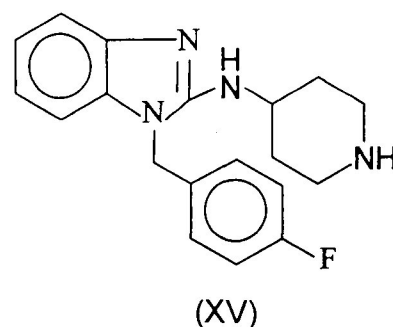
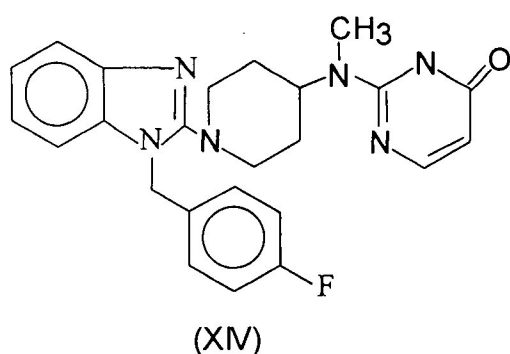


As both these fine chemicals are totally imported, at present there is a great need to develop a simplified preparative process from readily available raw materials. Taking into account the importance of these specific fine chemicals, their synthesis was included in the present work.

PART III :

Classic histamine H-1 antagonists are associated with sedative side effects. Taking this fact into consideration, the pharmaceutical industry has embarked upon the search for sedation free H-1 receptor compounds. As a result, over eleven non-sedating anti-histamines have been introduced over the last 12 years. At least seven histamine H-1 antagonists are in clinical trials. Speacor's Allegra, a non-cardiotoxic Terfenadine metabolite, was introduced in August 1999 in the U.S.A. It is available as capsules and is used for the relief of seasonal allergic rhinitis. Speacor's Norastemizole, a non-cardiotoxic metabolite of Astemizole, is in Phase-I clinical trials together with Dompe's DF-1111301, Hokuriker Seiyaku's HSR-609, UCB's Efluetrizine and Uriach's UR-12592.

A series of benzimidazoles was synthesized with the aim of obtaining a potent and non-sedative histamine H-1 receptor antagonist and compounds like Mizolastine(XIV) and Norastemisole(XV) were selected for further evaluation in view of their pharmacological profile.



A study carried out in rodents found (XIV) to be a highly selective and potent H-1 receptor antagonist. In a binding assay comparing (XIV) with seven other H-1 antagonists, (XIV) was ranked fourth in potency. Functional tests and binding assay demonstrated that (XIV) had high specificity for H-1 receptors

but not for serotonergic, noradrenergic and muscarinic cholinergic receptors. The antianaphylactic activity of (XIV) have been evaluated in rat, mouse, and guinea pig. The passive cutaneous anaphylactic reaction induced by an ovalbumin challenge in rats was inhibited by (XIV), as well as the lethal shock provoked by the compound. In guinea pigs, similar results were obtained, which effectively prevented morphological changes and inhibited anaphylactic mortality, bronchospasms and respiratory disturbances. In addition role of (XIV) in inhibiting the release of histamine in tissues during an allergic reaction and that its half life for pharmacological actions ranged from 6-8 hours has been proved and it was shown to be more effective than Loratidine and Terfenadine.

Astemizole, Cetirizine, Loratidine and Terfenadine demonstrated low sleep producing potential in rats, and it was suggested that their limited ability to cross the blood-brain barrier might be the reason for the low incidence of sedation in humans. In contrast, no sedative effects were manifested with (XIV), regardless of the route of administration utilized⁴⁰.

Intrinsic potency and selectivity for receptor subtypes was determined by competitive radioligand binding studies in isolated receptor preparations. By comparison, Astemizole had about 13 times less affinity for H-1 receptors, and 39 fold less potency against histamine induced contractions in guinea pig ileum. When *in-vivo* anti-histaminic activity was assessed using the guinea pig wheal and flare model, XV had to a rapid onset of action, showing activity 15-30 minutes after oral administration. Maximum activity was achieved between 30-60 minutes and did not decline upto 120 minutes. The relative potency of (XV) was found to be 20 times more potent than Astemizole, and 150 times more potent than Fexofenadine⁴¹.

Mizolastine and Norastemizole are potentially important additions to the class of third generation anti-histamines. They offer significant advantages over the second generation compounds in terms of potency, safety, onset and duration of action. Of these two drugs, (XIV) has been introduced in the U.K. as Mizollen by Lorex Synthelabo for the symptomatic relief of seasonal and

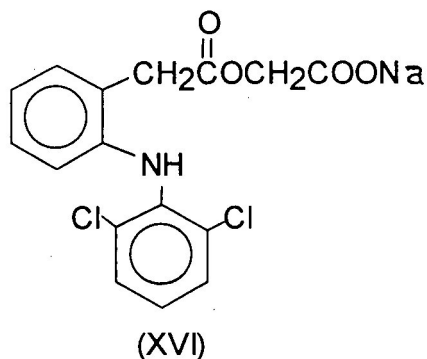
perennial allergic rhinoconjunctivitis and urticaria. The product is available as tablets, containing 10mg active drug⁴². The latter, (XV), is in advanced clinical development. Both are important therapeutic agents. Synthesis of both these drugs start from a common starting material 2-chloro 1-(4-fluorobenzyl) benzimidazole. Hence, synthesis of this vital drug intermediate was carried out in our laboratory by a different route to get improved results.

PART IV :

According to the new drug policy announced recently by the Government, there exists a great scope for the manufacture of bulk drugs in general, especially so for some of the drugs which are either not manufactured in India at present or those for which the requirement is exceedingly high as compared to the production.

The modern era of anti-rheumatic drugs began with the development of Aspirin in 1893 and has mushroomed into a bewildering group of agents. The benefits of a wide range of non-steroidal anti-inflammatory drugs lies in the fact that patients responses to therapy are unpredictable, and many agents may be tried before any clinical response is seen. Generally, agents having fewer side effects, particularly gastrointestinal, and agents with a longer half-life, are preferred.

Non-steroidal anti-inflammatory drugs are extensively used throughout the world in the treatment of a number of pathological conditions ranging from arthritis to dysmenorrhea, but several adverse effects limit their clinical usefulness. Among the most frequent complication is gastrointestinal lesions, and these are often responsible for discontinuance of therapy in patients taking NSAID's. Therefore, considerable effort was put in the search for effective NSAIDs with fewer adverse side effects. In order to obtain novel anti-inflammatory agents with improved gastrointestinal tolerance, a series of phenyl acetic acid derivatives were synthesized and screened. Among the synthesized compounds, Aceclofenac (XVI) showed potent anti-inflammatory activity.



Aceclofenac is a new orally effective non-steroidal agent possessing a potent inhibitory activity in several models of acute and chronic inflammation in rodents, and resembles Indomethacin and Diclofenac in its pharmacodynamic profile, which is superior to Naproxen and Phenylbutazone. In addition, (XVI) was found to be highly active against sodium urate-induced synovitis in dogs and adjuvant-induced polyarthritis in rats, both prophylactically and therapeutically. The analgesic effect of (XVI) on the pain elicited by chemical and mechanical stimuli, was nearly equal to or slightly better than that of Indomethacin and Diclofenac. Fever, induced by Brewer's yeast injection in rats was also markedly suppressed by (XVI). In contrast, the acute gastric ulcerogenic activity of (XVI) was about 2, 4 and 7 fold lesser than that of Naproxen, Diclofenac and Indomethacin, respectively. As a consequence of its high anti-inflammatory activity and lower potential for gastric damage, (XVI) exhibited the most favorable therapeutic ratio in comparison with Naproxen, Diclofenac, Indomethacin and Phenylbutazone. These data indicate that Aceclofenac is a potent anti-inflammatory and analgesic agent with a wide margin of safety in clinical practice⁴³.

Thus, the efficacy of (XVI) in the treatment of various conditions associated with the inflammatory process reflects its novel spectrum of actions⁴³.

Aceclofenac has not yet been taken up for the manufacturing in India³⁸. Hence there exist a good scope for manufacturing the bulk drug. With this view, it was planned to develop a laboratory process for its preparation, such that, it would be feasible and economical enough to be scaled up to the industry level.

Literature Survey

LITERATURE SURVEY

Part A

2-amino substituted benzophenones :

Investigations into the synthesis of various 1,4-benzodiazepinones revealed a wide range of methods. All started with an appropriately substituted o-aminoketone. Hence, medicinal chemists intending to synthesize 1,4-benzodiazepinones essentially had to bear with the arduous task of preparing the O-aminoketone.

Since the preparation of O-aminoketone was mandatory, a large number of methods were devised to synthesize them. There was, however, not a single method which had the facility of operation, versatility of substituents and good yields. All the reported methods lacked some of the above qualities.

By and large, there are two approaches to 2-amino substituted benzophenones. One route uses the friedel-crafts reaction of p-chloroaniline with benzoyl chloride and the other involves reductive cleavage of 5-chloro-3-phenyl-2,1-benzisoxazole to give the o-aminoketone.

Method 1 :

The first method reported by Sternbach et al⁴⁴ is a classical friedel-crafts acylation reaction involving benzoylation of p-substituted aniline. p-chloroaniline is heated with 2-halo substituted benzoylchloride in the presence of Aluminum chloride and the resultant dimer is hydrolyzed with acid to give 2-amino substituted benzophenone. The method, however, involves two steps, the second step, which is hydrolysis of the dimer, formed by simultaneous C and N benzoylation, being difficult. This also accounts for poor yields.

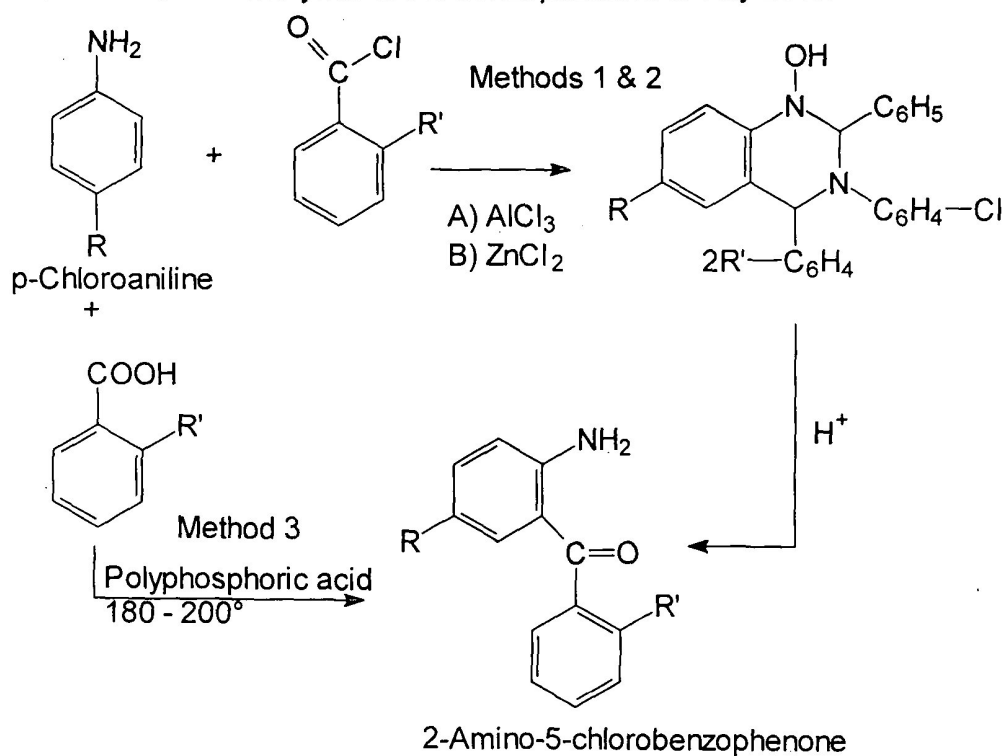
Method 2⁴⁵⁻⁴⁹ :

Benzoylation reaction of p-chloroaniline and benzoylchloride using anhydrous zinc chloride to obtain the title o-aminoketone has been reported in several communications.

In one of the procedures, p-chloroaniline is added portionwise during 25 minutes to benzoylchloride heated to 132°C. This mixture is heated to 190° and the anhydrous zinc chloride is added at this temperature over a period of 40 minutes. The mixture is further heated to 200°C for one hour. This mixture is then cooled to 100°C and extracted with boiling water. Benzoic acid is separated from the aqueous extract to give the solid condensation product 2,4-diphenyl-3-p-chlorophenyl-4-hydroxy-3,4-dihydro-6-chloroquinazoline. This is hydrolyzed at 120-130°C during 6-8 hours with acetic acid and sulfuric acid. The hot reaction mixture after hydrolysis is poured into ice and the precipitated benzoic acid is separated. The residue is treated with another portion of ice water to give the o-aminoketone.

Method 3⁵⁰ :

Equimolar amounts of arylamine(I) and carboxylic acid was condensed to furnish aminobenzophenones on heating with excess polyphosphoric acid solution at 180-200°C. The yield of the benzophenone is only 20%.



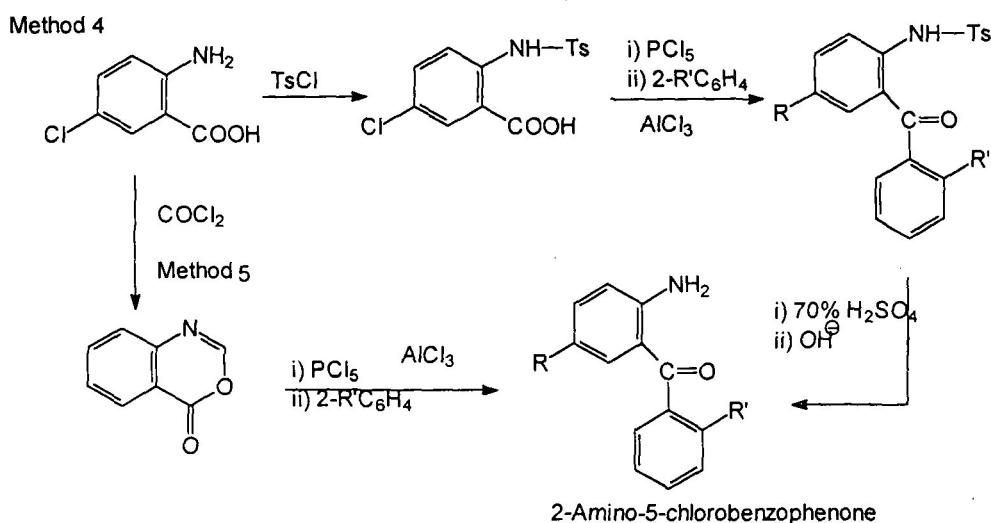
Method 4⁵¹ :

The starting material is a substituted anthranilic acid. The amino group of the acid is protected by a typical Schautten-Bauman method. The carboxylic acid

function is then converted to acid chloride with phosphorus pentachloride and an appropriate substrate of benzene is acylated using a Lewis acid. The tosyl group is knocked out either by the conventional method of boiling with 70% sulfuric acid or by warming with a 1:1 mixture of glacial acetic acid and perchloric acid.

Method 5⁵² :

Another method for the synthesis of substituted o-aminobenzophenone reports the use of a substituted anthranilic acid, but follows a totally different route. It involves the preparation of isocyanatobenzoyl chloride from anthranilic acid by treatment with phosgene and simultaneously phosphorus pentachloride. A Friedel-Crafts acylation reaction is carried out using benzene as the substrate. The method fails to give good yields and involves the use of a hazardous gas like phosgene.

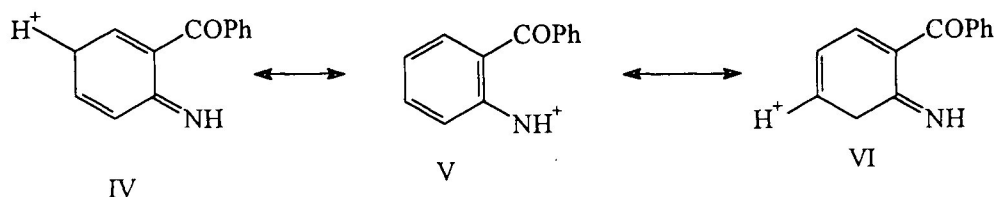
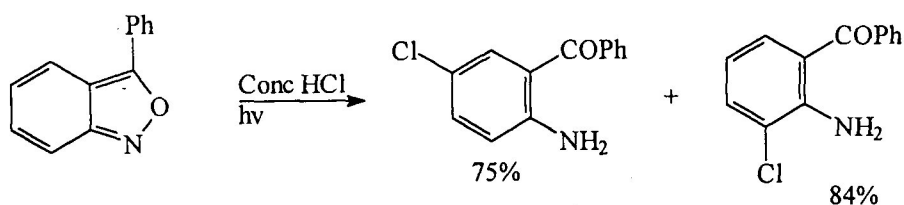
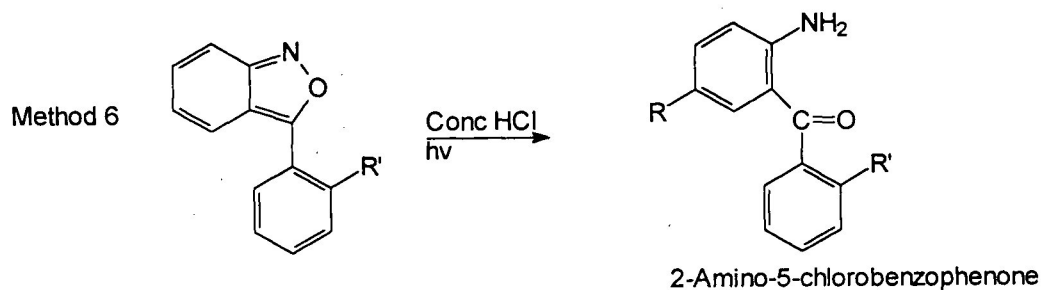


Method 6⁵³ :

Photo-induced nucleophilic substitution of 3-substituted-2,1-benzisoxazoles (under ring opening conditions) gives 2-aminobenzophenone. UV-irradiation of 3-aryl-2,1-benzisoxazole in concentrated hydrochloric acid gives aminobenzophenone.

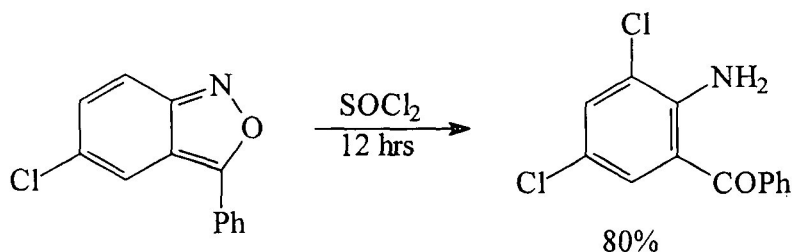
Another report⁵⁴ mentions that photolysis of the substituted benzisoxazole in concentrated hydrochloric acid gives a mixture of 2-amino-5-chloro and 2-amino-3-chlorobenzophenone in 75% and 84% yields, respectively. The

reaction takes place via protonation of N followed by cleavage of the N-O bond to give the cation intermediate ($IV \leftrightarrow V \leftrightarrow VI$) which undergoes nucleophilic attack by Cl^- at the electrophilic carbon atoms.



Method 7⁵⁵ :

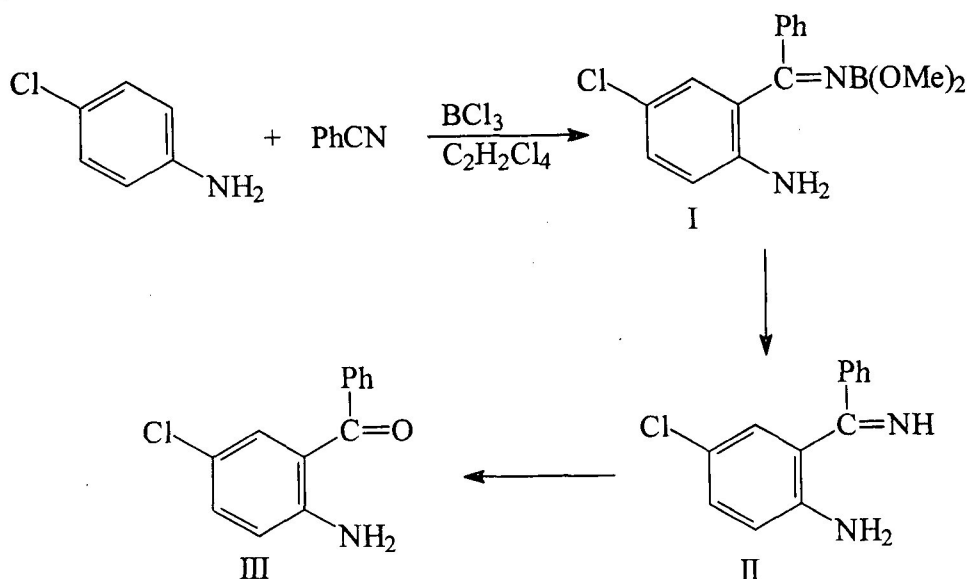
In a novel reaction of thionyl chloride with 3-aryl-2,1-benzisoxazole, mixing 5-chloro-3-phenyl-2,1-benzisoxazole with excess thionyl chloride and allowing it to stand for 12 hours gives 3,5-dichloro-2-aminobenzophenone in a 80% yield.



Method 8⁵⁶ :

Refluxing p-chloroaniline with tetrachloroethane or benzene and benzonitrile in presence of borontrichloride gives the halo-o-aminoketone. The reaction

takes place in stages. Thus, the reaction of p-chloroaniline with benzonitrile first gives I, then II and finally III



Method 9⁵⁷ :

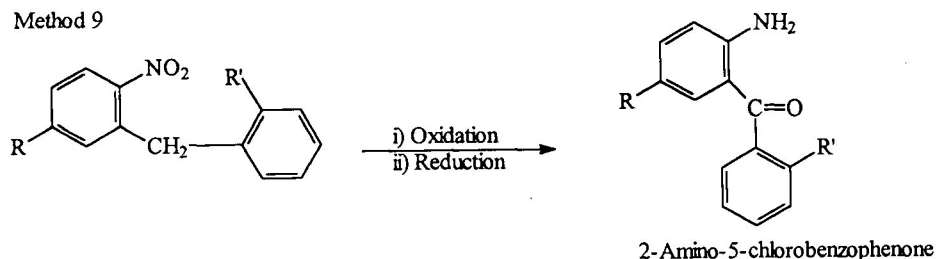
The title intermediate can be synthesized by oxidation and subsequent reduction of the o-nitrodiphenyl methane. The method, however, is only of academic interest since it gives very poor yields.

Method 10⁵⁸ :

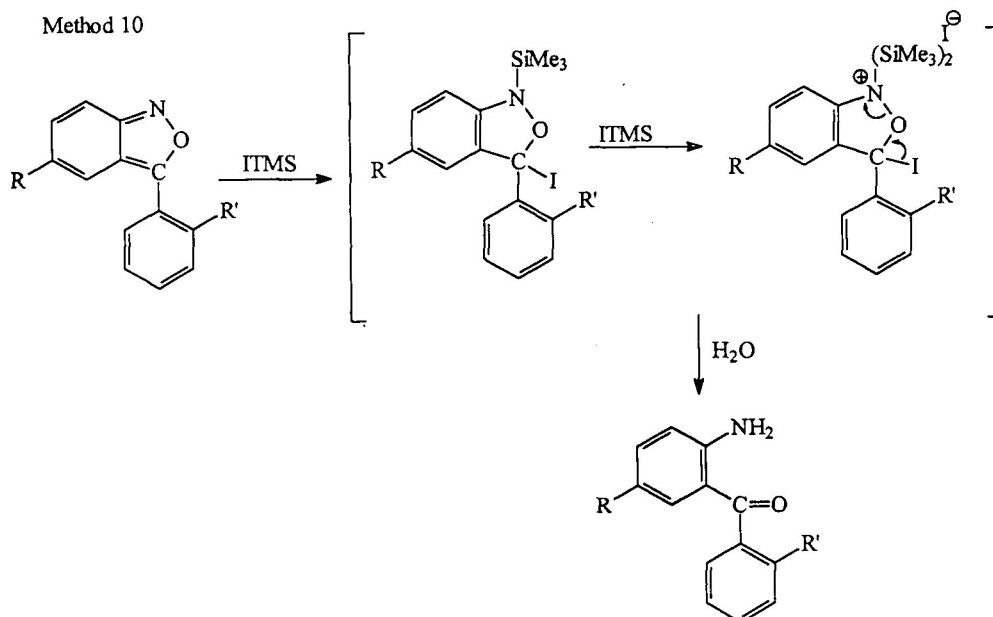
In a novel procedure, 5-chloro-3-phenyl-2,1-benzisoxazole undergoes reductive cleavage with iodotrimethyl silane (prepared in-situ) to yield 2-amino-5-chlorobenzophenone. A mixture of chlorotrimethylsilane and sodium iodide in chloroform is stirred for 45 minutes. To this mixture is added the benzisoxazole and stirred at room temperature for 2 hr. The reaction mixture is treated with distilled water and further stirred for 1 hr. The organic layer yields 2-amino-5-chlorobenzophenone in 92% yield.

Regarding the mechanism of this novel transformation, it appears that two molecules of iodotrimethyl silane are involved. One molecule adds across the heterodiene system and second molecule attacks further to give quarternary salt, which is ruptured by aqueous work up.

Method 9



Method 10



Method 11⁵⁹ :

This route to 2-aminobenzophenones involves the reductive cleavage of 2,1-benzisoxazole ring in the presence of conventional reducing agents, such as metal acid combinations. Reduction of the anthranil has been carried out using various metal acid combinations and catalytically using Palladium on charcoal catalyst. The method using Palladium gives quantitative yield of the ketone. The scale of operation is limited only by solubility of the material in the solvents used, eg. Ethyl acetate.

5-chloro-3-phenyl-2,1-benzisoxazole is reduced with iron in acetic acid at 80-110°C to give o-aminoketone in good yields^{51,54,60}.

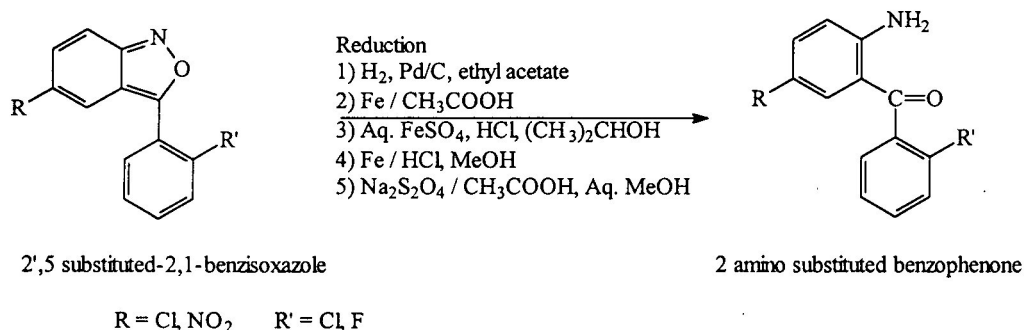
Another method⁶¹ utilizes isopropyl alcohol as the reaction medium. Refluxing anthranil with ferrous sulphate and hydrochloric acid in the presence of alcohol for 3 hr. gives o-aminoketone in good yields.

In a slight variation⁶² of the above procedure, a mixture of anthranil, iron, hydrochloric acid and methanol is refluxed for 3 hrs. to give 2-aminobenzophenone.

A patent⁶³ describes the use of a 2-3 fold molar excess of sodium dithionite in acetic acid and aqueous methanol to give o-aminoketone in 89.4% yield.

Attempts to synthesize the benzodiazepines without going through the o-aminoketone step were made by Japanese chemists at the Sumitomo Co. They synthesized indole derivatives of the type shown, which on oxidation of the double bond formed the aminoacetamido compound that cyclized under the reaction conditions. However, the method again involved the synthesis of appropriate indole molecule.

Method 11



Part B

Systematic reviews on benzimidazoles were published in 1951⁶⁴ and 1953⁶⁵ although subsequent surveys have appeared in articles^{66,68} covering the chemistry of both imidazoles and benzimidazoles. In the recent reviews⁶⁹, a compilation of the synthesis, reactions and spectroscopic properties of benzimidazoles is presented.

General methods

Synthesis of benzimidazoles starts practically with O – phenylene diamine. In the literature survey, we have come across the following methods used for the synthesis of benzimidazoles :

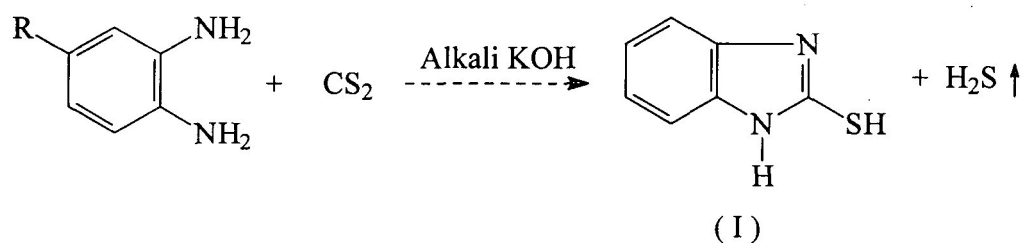
- by reacting *o* – phenylene diamines with carboxylic acids^{70,71}.
- by reacting *o* – phenylene diamines with acid chlorides^{72, 73}, ester⁷⁴ or acid anhydride⁷⁵.
- by reacting *o* – phenylene diamines with amide⁷⁶ or nitrile⁷⁷.
- by reacting *o* – phenylene diamines with aldehyde⁷⁸ or ketone⁷⁹.
- by reacting *o* – phenylene diamines with urea⁸⁰ or thiourea⁸¹.
- by reacting *o* – phenylene diamines with isothiocyanate⁸².

2 – mercapto benzimidazole

a) Synthesis from *o* – phenylene diamine and carbondisulphide

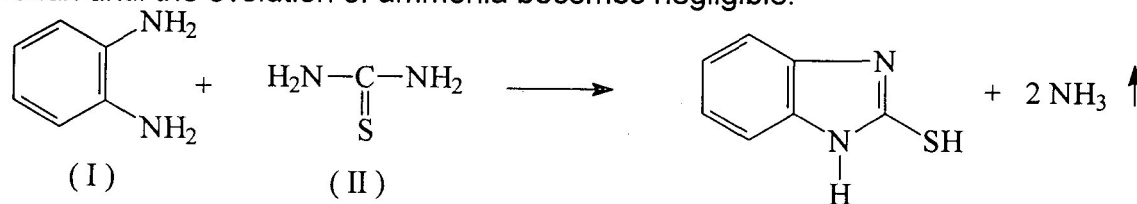
2 – mercapto benzimidazole, in general, may be prepared very conveniently by this method. The reaction is carried out usually by heating the reactants in alcoholic solution, with or without the addition of alkali to the reaction mixture.

2 – mercapto benzimidazole itself has been prepared by this method^{83,84}.



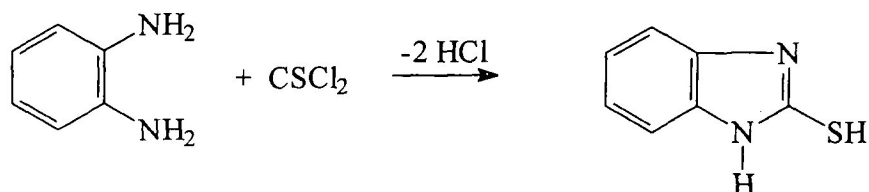
b) Synthesis from *o* – phenylene diamine and thiourea

This reaction is analogous to the preparation of 2 – hydroxy benzimidazole from *o* – phenylene diamines and urea. 2 – mercapto benzimidazoles may be prepared by this method by heating substituted *o* – phenylene diamine dihydrochloride (I) and thiourea (II) to 170 – 180°C⁸⁵. Excellent yields have been obtained by carrying out the reaction in amyl alcohol and heating under reflux until the evolution of ammonia becomes negligible.



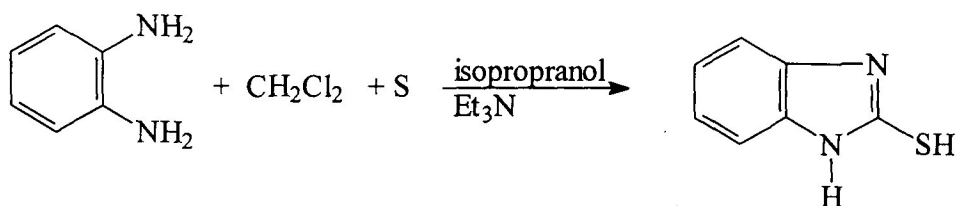
c) Synthesis from O – phenylene diamine and thiophosgene

Billeter and Steiner⁸⁶ obtained 2 – mercapto benzimidazole and 5 – methyl – 2 – mercapto benzimidazole by action of thiophosgene on O – phenylene diamine and 3, 4 – diamino toluene, respectively. 3, 4 – diamino benzene arsenic acid and thiophosgene gave 78 % yield of 2 – mercapto – S – arsenic acid benzimidazole⁸⁷.



d) Synthesis from O-phenylene diamine, dichloromethane and sulfur

2-mercaptobenzimidazole is prepared by heating O-phenylenediamine with dichloromethane and sulfur in isopropanol at in the presence of triethylamine. This gives 2-mercaptobenzimidazole in 93% yield⁸⁸.



e) Miscellaneous methods

2 – mercapto benzimidazole can be prepared in 84 – 86.5 % yield by the action of potassium ethyl xanthate on O – phenylene diamine⁸⁹. 2 – mercapto benzimidazoles have also been prepared from O – phenylene diamine dihydrochloride and ammonium thiocyanate. A solution of the two substances is usually evaporated to dryness on a steam bath and then heated for a short period of time.

Synthesis of 2-chloro-1(4-fluorobenzyl) benzimidazole :

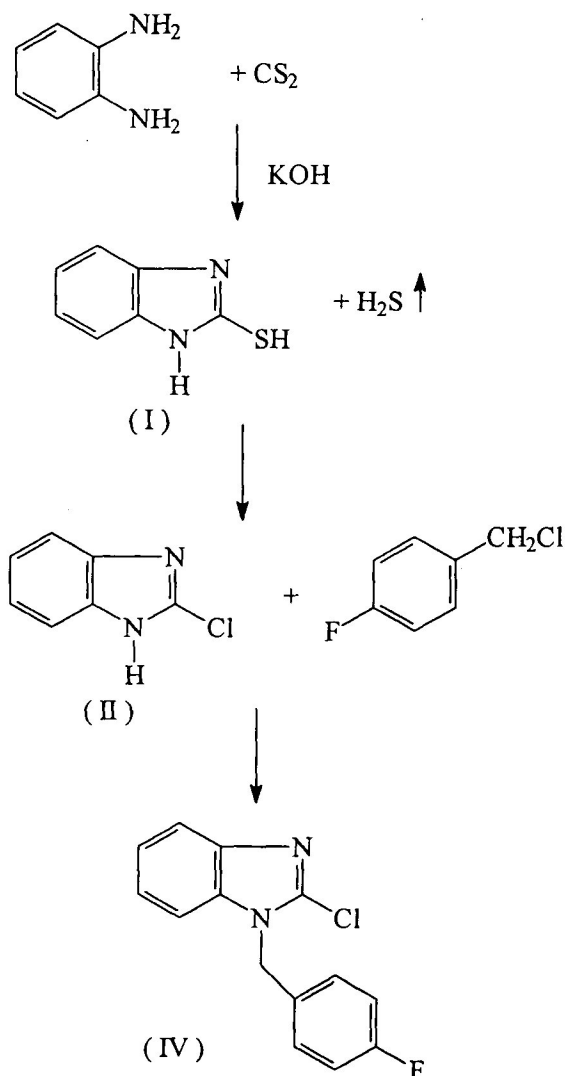
Method 1 :

O-phenylenediamine was cyclized with carbon disulfide in the presence of alcoholic solution of alkali to give 2-mercapto benzimidazole(I). Chlorination of (I) was carried out by suspending (I) in chloroform and water mixture, which was cooled to 5°C. A slow stream of chlorine was bubbled through the solution for one hour while maintaining the temperature. At the end of this, the reaction mixture was transferred to evaporating dish to expel excess chlorine. Evaporation of the solvent afforded a sticky mass. Passage of the material through silica gel column and elution with chloroform gave 2-chlorobenzimidazole(II). Alkylating (II) with 4-fluorobenzyl chloride under strong basic condition (NaH 80%, DMF, 60°C) gave the title compound(IV)⁹⁰.

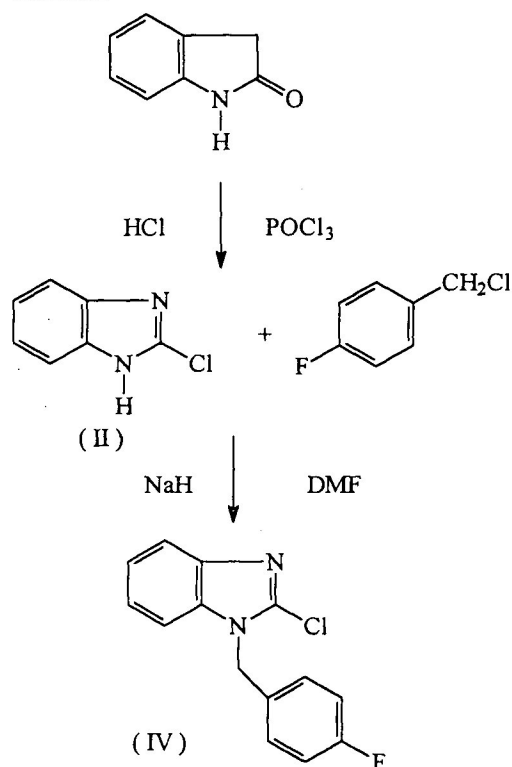
Method 2 :

In this method, benzimidazolin-2-one was boiled under reflux with phosphoryl chloride for 3.5 hr. and hydrochloric acid gas was passed for the last 3 hr. Excess phosphoryl chloride was removed under reduced pressure and the residue was treated with ice cold water. Cold acid suspension was filtered and washed with water and the filtrate was treated with ammonia. This afforded (II). A mixture of (II) and sodium hydride in DMF was stirred at 60°C for 1 hr. Then, 4-fluorobenzyl chloride was added and the reaction mixture was heated for 5 hr. After cooling to room temperature, the mixture was poured in cold water. The precipitate obtained was filtered and purified by column chromatography⁹¹⁻⁹².

Method 1



Method 2

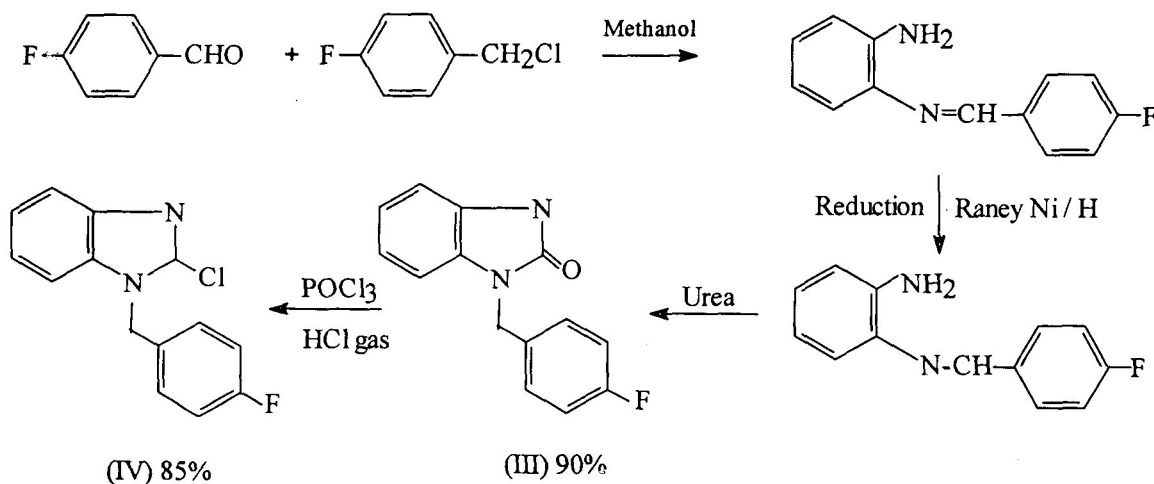


Method 3 :

A mixture of 2-hydroxy benzimidazole and phosphoryl chloride was heated to reflux for 4 hr. Excess phosphoryl chloride was removed under vacuum and the residue was treated with cold water. The cold water mixture was filtered, washed with water and then treated with dilute hydrochloric acid. The filtrate and washings were made alkaline with diluted ammonium hydroxide. The precipitated product was collected by filtration and recrystallised with aqueous ethanol to give (II), alkylation of (II) with 4-fluorobenzyl chloride under strong basic conditions afforded (IV)^{92,93}.

Method 5 :

A solution of 4-fluorobenzaldehyde in methanol was kept in ice bath and the precipitate obtained was isolated and combined with second portion obtained on concentration of mother liquor to yield N-(4-fluorobenzal) O-phenylenediamine. Reduction of this compound with hydrogen in the presence of Raney nickel using dioxane at 130 atmosphere and at 70-75°C followed by filtration and evaporation of solvent below 35°C gave N-fluorobenzyl-O-phenylene diamine. Heating with urea at 170-180°C gives the substituted benzimidazolinone, which was refluxed with phosphorous oxychloride to give (IV) in 85% yield⁹³⁻⁹⁴.

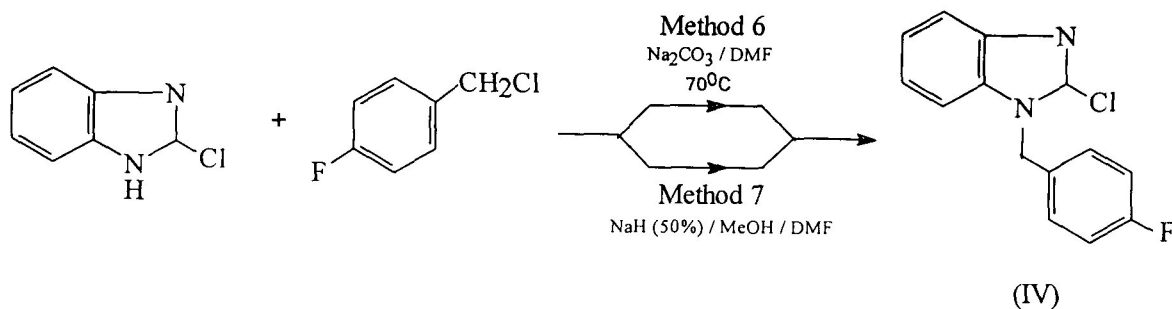


Method 6 :

Another method for preparation of 2-chloro-1-(4-fluorobenzyl)benzimidazole (IV) involves use of weak basic conditions (Na₂CO₃, DMF) at 70°C⁹⁷.

Method 7 :

This method states that ring alkylation of 2-chlorobenzimidazole occurs under strong basic conditions using 50% NaH, dimethyl sulfoxide and benzene as solvent⁹⁷.



Part D

Synthesis of Aceclofenac :

One convenient method by which Aceclofenac can be synthesized is through esterification of diclofenac sodium with halo substituted acetic acids. Since the discovery of Diclofenac sodium as an anti-inflammatory agent, many methods have been reported for its synthesis. However most of these methods are covered by the international patents. Various reported methods are discussed below :

Method 1^{98,99} :

In this method a mixture of 2,6-dichloroacetanilide, bromobenzene, potassium carbonate and copper is refluxed for 48 hr. The crude N-(2,6-dichlorophenyl)-N-phenylacetamide(I) formed, is hydrolyzed with 10% ethanolic KOH to give 2,6-dichlorodiphenylamine(II). Heating (II) with chloroacetyl chloride gave the N-chloroacetyl derivative (III). Heating together (III) and AlCl_3 at 160°C for 2 hr. and pouring onto ice gave 1-(2,6-dichlorophenyl)-2-indolinone (IV). Hydrolysis of (IV) with alcoholic NaOH gave Diclofenac.

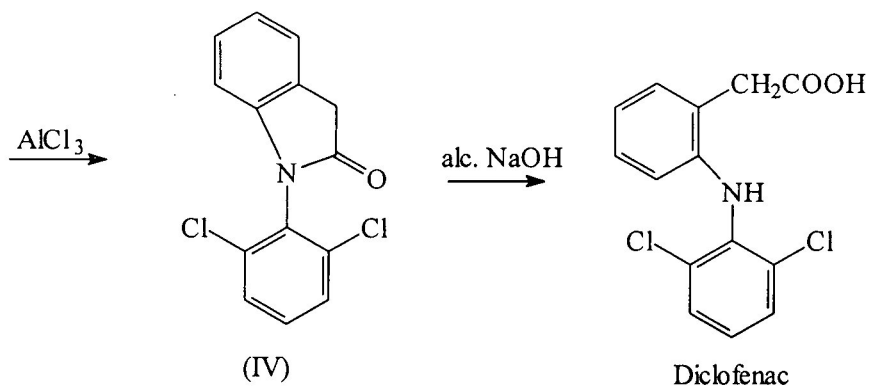
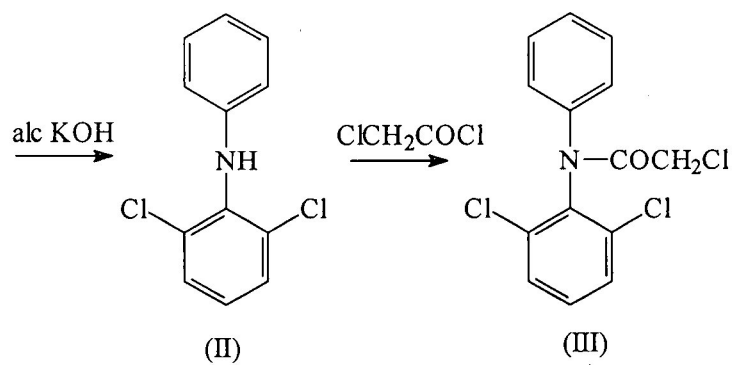
In a similar reported method, 2,6-dichlorodiphenylamine(I) was synthesized by decarboxylation of N-(2,6-dichlorodiphenyl)-anthranilic acid¹⁰⁰.

Method 2¹⁰¹⁻¹⁰³ :

α -Bromobenzoic acid and 2,6-dichloroaniline were treated to give N-(2,6-dichlorophenyl)anthranilic acid(I), which was heated to give 2,6-dichlorodiphenylamine(II). (II) was treated with oxalylchloride, followed by AlCl_3 to give 1-(2,6-dichlorophenyl)indole-2,3-dione(III). To (III) in glyme was added hydrazine hydrate, powdered KOH and slowly heated to 150° and kept at that temperature for 1 hr. to give Diclofenac.

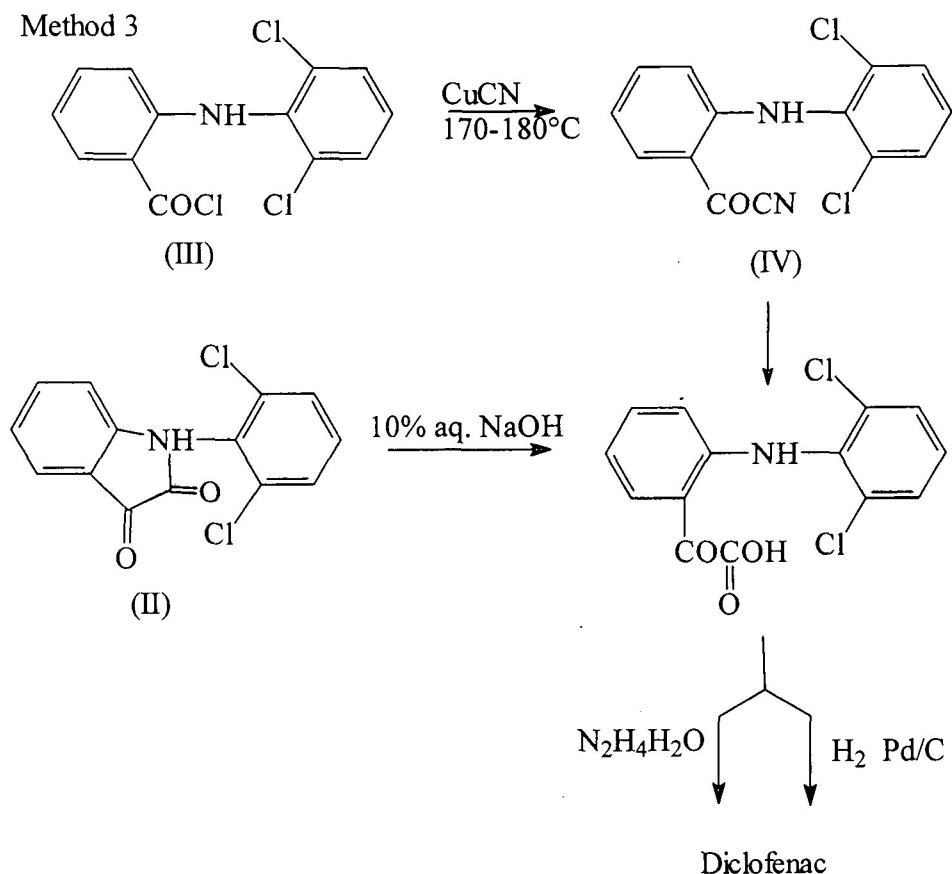
CC(=O)Nc1cc(Cl)ccc1Cl.CBr>>CC(=O)N(c1ccccc1)c2cc(Cl)ccc2Cl

(I)



Method 3 :

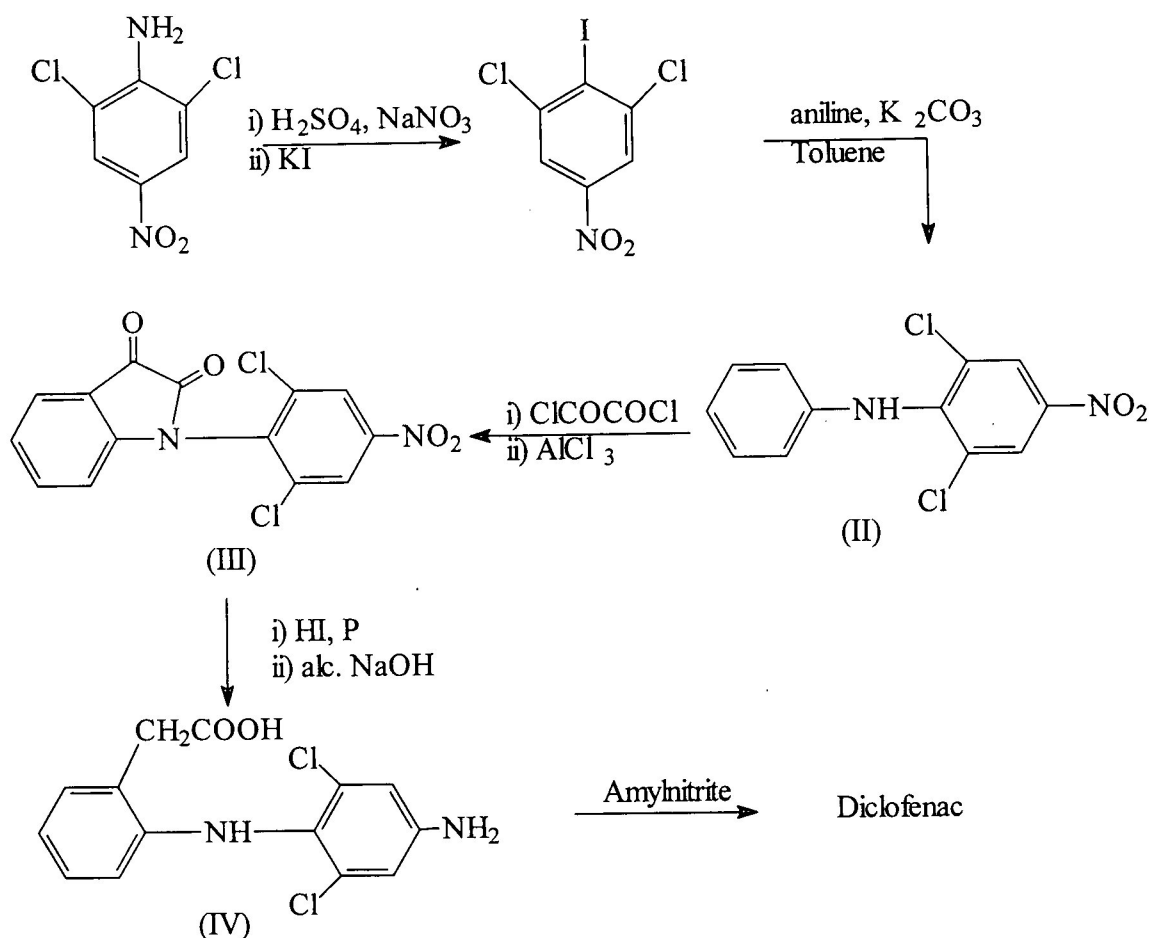
In this method Diclofenac is synthesized by reduction of 2-(2,6-dichloroanilino) phenylglyoxylic acid(I) either by wolf-Kishner method ^{104,105} or by hydrogen over 10% Pd/C¹⁰⁶. (I) was prepared by hydrolysing 1-(2,6-dichlorophenyl)-indole-2,3-dione(II) with 10% aqueous NaOH in ethanol for 3 hr. and acidifying¹⁰⁶. In another method of preparation of (I), N-(2,6 - dichlorophenyl)anthraniloyl chloride(III) is treated with CuCN for 15 min. at 170-180°C to give N-(2,6-dichlorophenyl) anthraniloyl cyanide(IV), which on hydrolysis with conc. HCl gave (I)¹⁰⁷.



Method 4¹⁰⁸⁻¹¹¹ :

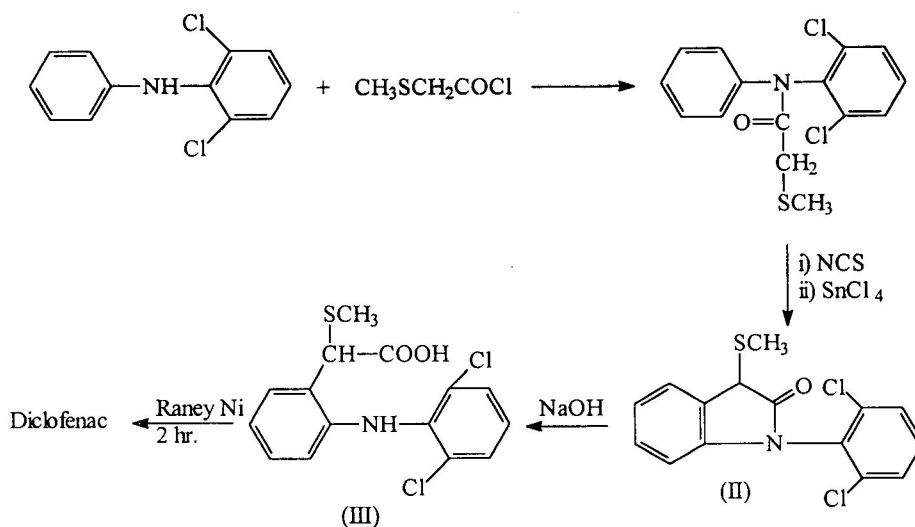
2,6-dichloro-4-nitroaniline is diazotised and iodinated with potassium iodide to give 2,6-dichloro-4-nitroiodobenzene(I). (I) is aminated with aniline and potassium carbonate in toluene for 10 hr. to give 2,6 -dichloro-4-nitrodiphenylamine(II). N-acylation of (II) by oxalylchloride followed by Friedel-Crafts acylation-cyclization gives 1-(2,6-dichloro-4-nitrophenyl)-indoline-2,3-dione(III). Reduction of (III) with HI & P and hydrolysis with alcoholic NaOH gives (IV) which on diazotisation with amyl nitrite gives Diclofenac.

Method 4



Method 5¹¹²:

2,6-dichlorodiphenylamine is acylated with thiomethyl acetylchloride for 4 hr. to give (I), which is refluxed with N-chloro succinimide and SnCl_4 to give (II). This is refluxed with NaOH to give (III), which is refluxed with Raney Nickel in ethanol for 2hr. to give Diclofenac.



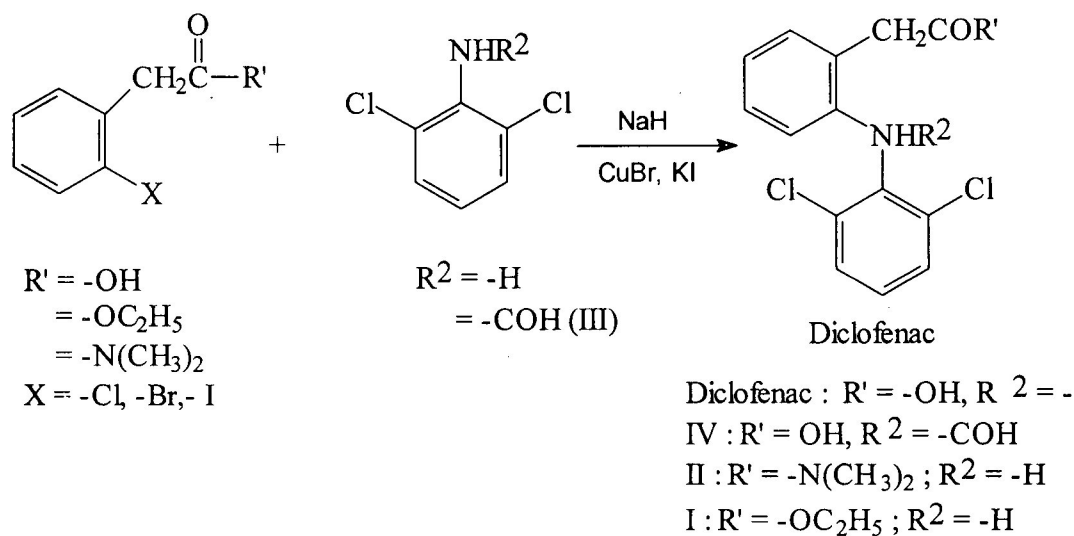
Method 6 :

In this method, o-halophenylacetic acid is condensed with 2,6-dichloroaniline in a high boiling solvent in the presence of copper and potassium carbonate to give Diclofenac¹¹³⁻¹¹⁷.

In a similar method, ester^{118,119} or amide¹²⁰ of o-halophenylacetic was condensed with 2,6-dichloroaniline and the condensation product (I) and (II), was hydrolyzed to give Diclofenac.

In a similar method o-halophenylacetic acid was condensed with N-(2,6-dichlorophenyl)formamide(III) in a high boiling solvent, in the presence of copper and K₂CO₃. The condensation product (IV) was hydrolyzed to give Diclofenac^{121,122}.

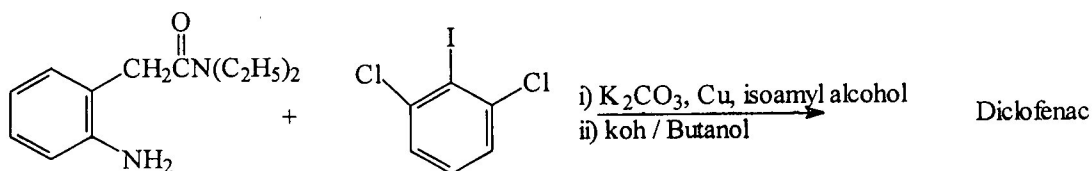
A condensation reaction of 2,6-dichloroaniline and o-bromophenylacetic acid was also carried out in the presence of a strong base sodium hydride and catalyst such as CuBr and KI¹²³.



Method 7 ¹²⁴:

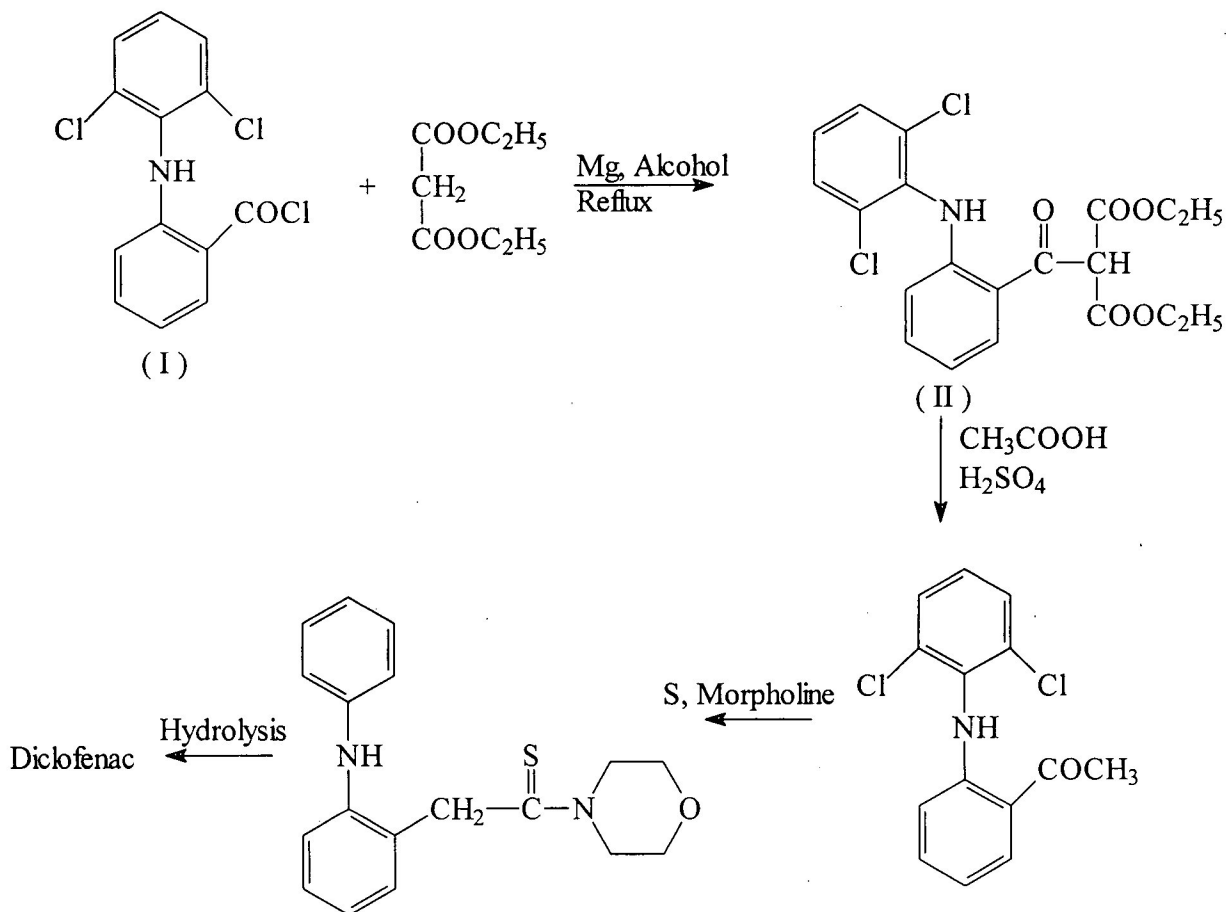
A mixture of N,N-diethyl-O-aminophenylacetamide and 2-iodo-1,3-dichlorobenzene in isoamyl alcohol is refluxed for 30h. to give an oil which was refluxed with 8ml water and KOH in butanol for 4h. to give Diclofenac.

Method 7



Method 8 ¹²⁵:

To a mixture of abs ethanol and carbon tetrachloride, Mg filings are added. The mixture is diluted with ether. To this diethylmalonate in abs ethanol is added. The mixture was refluxed for 3h. at 95°C. N-(2,6-dichlorophenyl)anthraniloyl chloride(I) in ether is added and the mixture refluxed and worked up to give diethyl [N-(2,6-dichlorophenyl) anthraniloyl] malonate(II). A mixture of acetic acid, conc.H₂SO₄ and H₂O was added to this and the mixture refluxed to give o-(2,6-dichloroanilino)acetophenone(III). A mixture of (III), sulfur and morpholine was refluxed to give 4-{ [o-(2,6-dichloroaniline)phenyl] thioacetyl }morpholine(IV). This on hydrolysis gave Diclofenac.

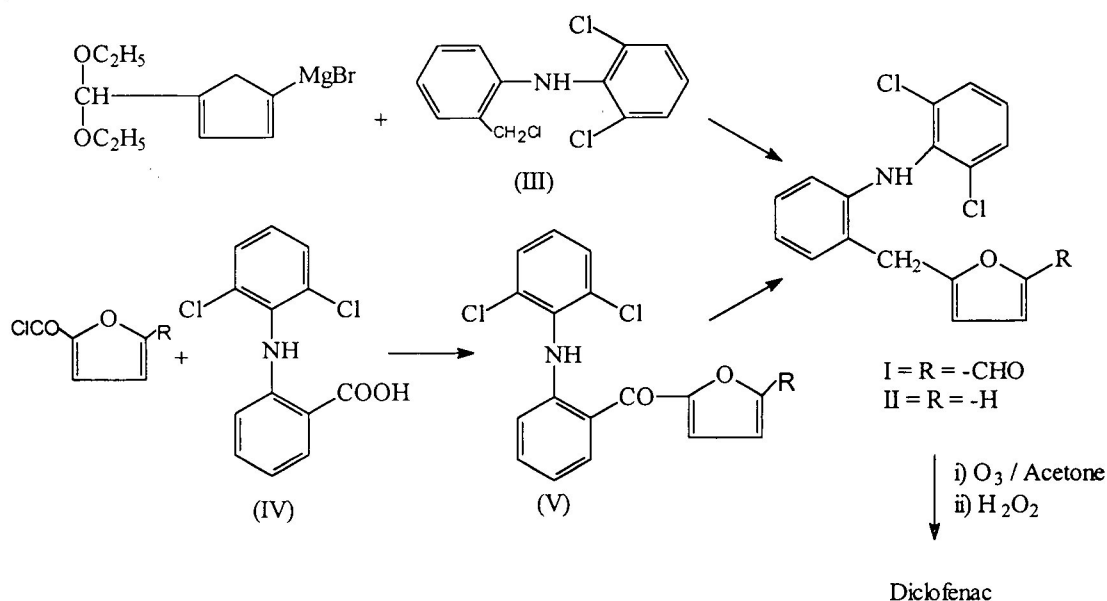


Method 9 :

5-[o-(2,6-dichloroanilino)benzyl] furfural(I) or 2-[o-(2,6-dichloroanilino)benzyl]furan(II) were ozonized in acetone and treated with H_2O_2 in aqueous sodium hydroxide to give Diclofenac¹²⁶⁻¹²⁸.

(I) was prepared by reaction of grignard reagent of 5-bromofurfuraldiethylacetal and 2,6-dichloro-2'-(chloromethyl) diphenylamine (III)¹²⁶.

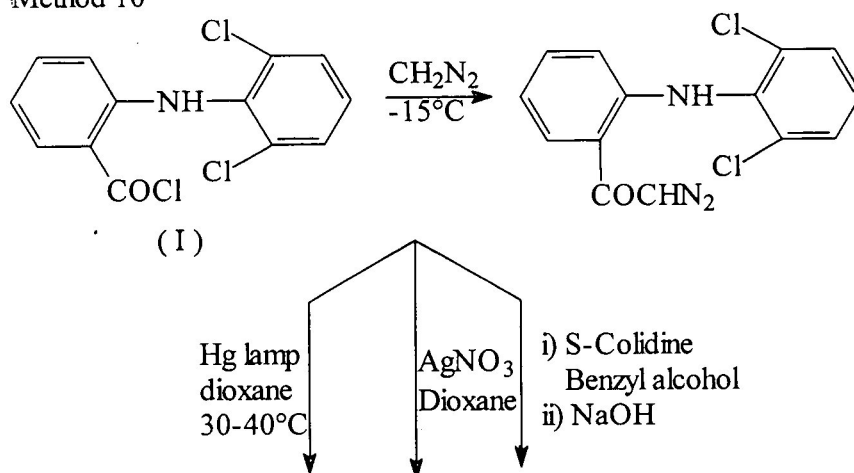
(II) was synthesized by metalizing furan with butyllithium, and then treating with N-[o-(2,6-dichloroaniline)benzoyl] furan(V). (V) on Wolf-Kishner reduction gives (II)¹²⁷.



Method 10^{129,130} :

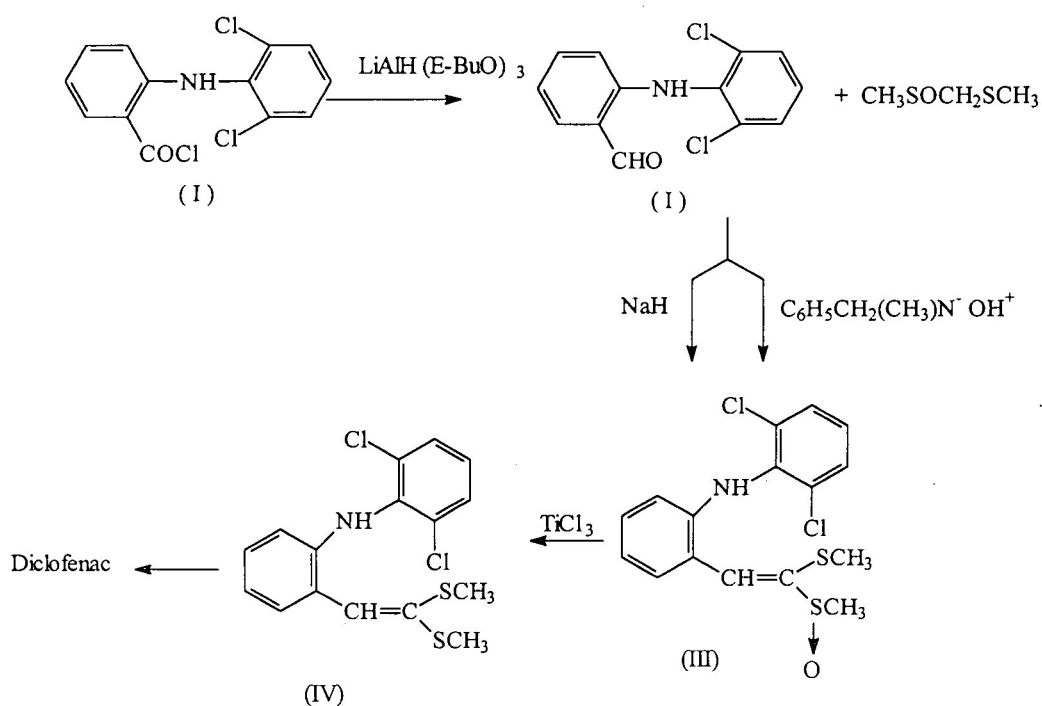
N-(2,6-dichlorophenyl)anthraniloyl chloride(I) and diazomethane in ether were left for 24hr. at -15°C to get the diazoketone(II) which in dioxane-water was stirred at $30-40^\circ\text{C}$ with mercury lamp irradiation and treated with NaOH to give, Diclofenac. Diclofenac was also prepared by heating (II) in dioxane-water with silver nitrate and subsequent NaOH treatment. In another method, a mixture of s-coldidine and benzyl alcohol were added to (II), the mixture stirred for 2-3hr. at 100°C . NaOH in 1:1 ethanol:water is added, and the whole mixture is refluxed for 3hr. to give Diclofenac.

Method 10



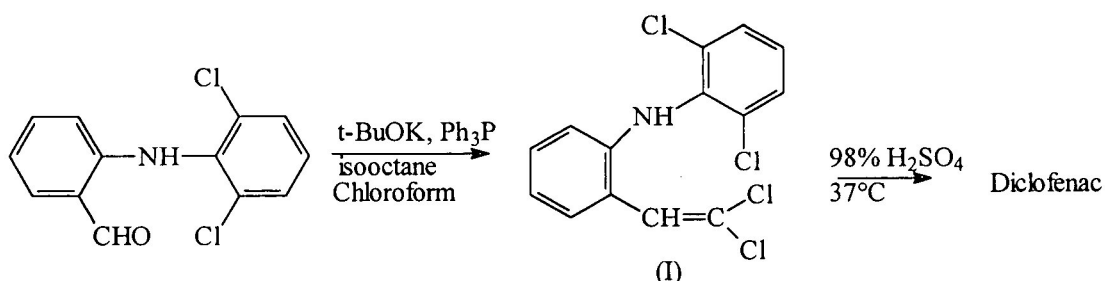
Method 11^{131,132}:

o-(2,6-dichloroanilino)benzaldehyde(II) prepared from the acid chloride by LiAlH (t-BuO)₃, was condensed with methylsulfinylmethylsulfide in the presence of sodium hydride¹³² or trimethyl benzyl ammonium hydroxide¹³¹ which gave (III). Reduction of (III) with TiCl₃ gave 1,1-bis(methylthio)-2-[o-(2,6-dichloroaniline)phenyl]ethylene(IV). Hydrolysis of (IV) with hydrochloric acid gives diclofenac.



Method 12^{133,134} :

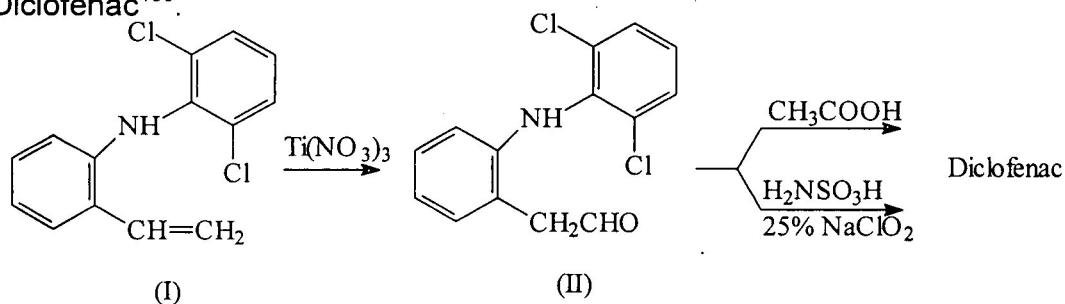
Chloroform in isooctane was added to a mixture of potassium t-butoxide and triphenylphosphine in isooctane. To this o-(2,6-dichloroanilino) benzaldehyde was added and stirred for 2 hr. with ice cooling and 43 hr. at room temperature to give 1-([2-(2,6-dichloroanilino)phenyl]-2,2-dichloroethylene(I). Stirring (I) with 98% sulfuric acid at 37°C gives Diclofenac.



Method 13 :

1-([2-(2,6-dichloroanilino)phenyl]ethylene(I) was stirred with $\text{Ti}(\text{NO}_3)_3$ in methyl alcohol at room temperature to give o-(2,6-dichloroanilino)phenylacetaldehyde(II). (II) was oxidized with acetic acid to give Diclofenac¹³⁵.

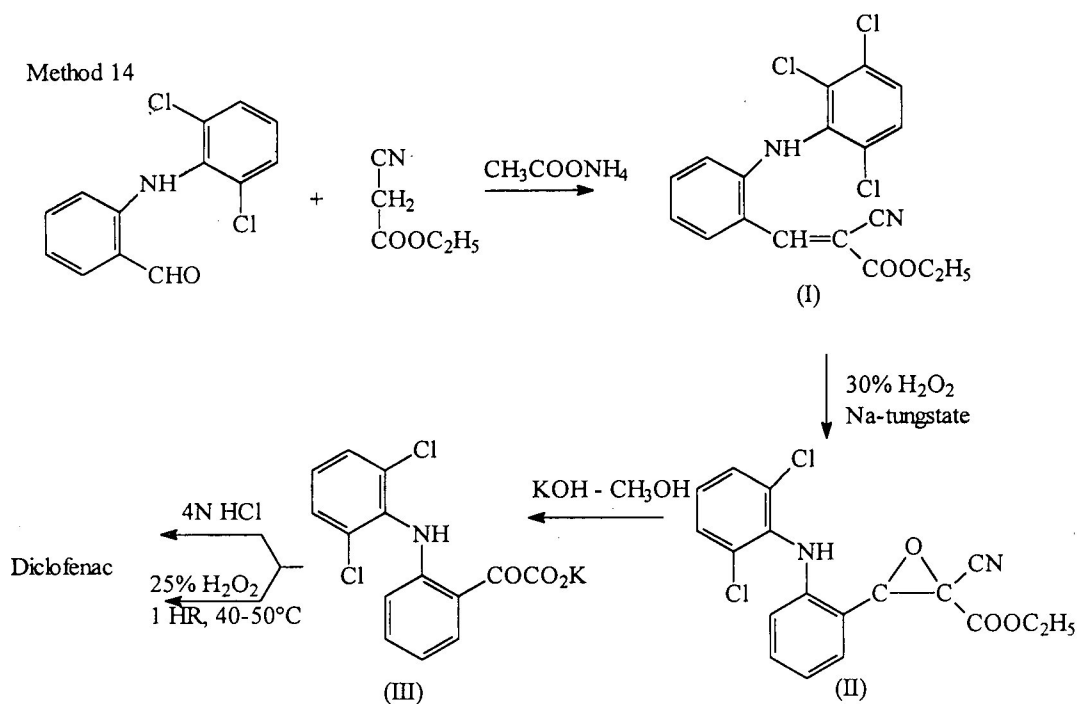
In another method (II) was oxidized by adding 2.5% aqueous sulfamic acid and 25% sodium chlorite at room temperature and stirred to give Diclofenac¹³⁶.



Method 14 :

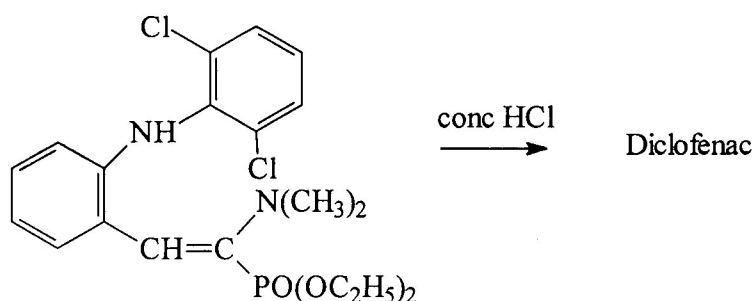
Refluxing o-[(2,6 dichlorophenyl)amino]benzaldehyde with ethyl cyanoacetate and ammonium acetate in benzene with removal of water gave (I). Epoxidation of (I) with 30% H_2O_2 and sodium tungstate in ethanol for 2 hr. gave (II). Refluxing of (II) with $\text{KOH-CH}_3\text{OH}$ for 1hr. at room temperature gave (III). (III) was treated with 4N HCl at low temperature and for 30 min. at room temp. to give diclofenac^{137,138}. (III) was alternatively oxidized with 25% H_2O_2 in water for 1hr. at 40-50°C to give diclofenac¹³⁹.

Method 14



Method 15¹⁴⁰ :

Product (I) on refluxing with conc. HCl for 3hr. gives Diclofenac.

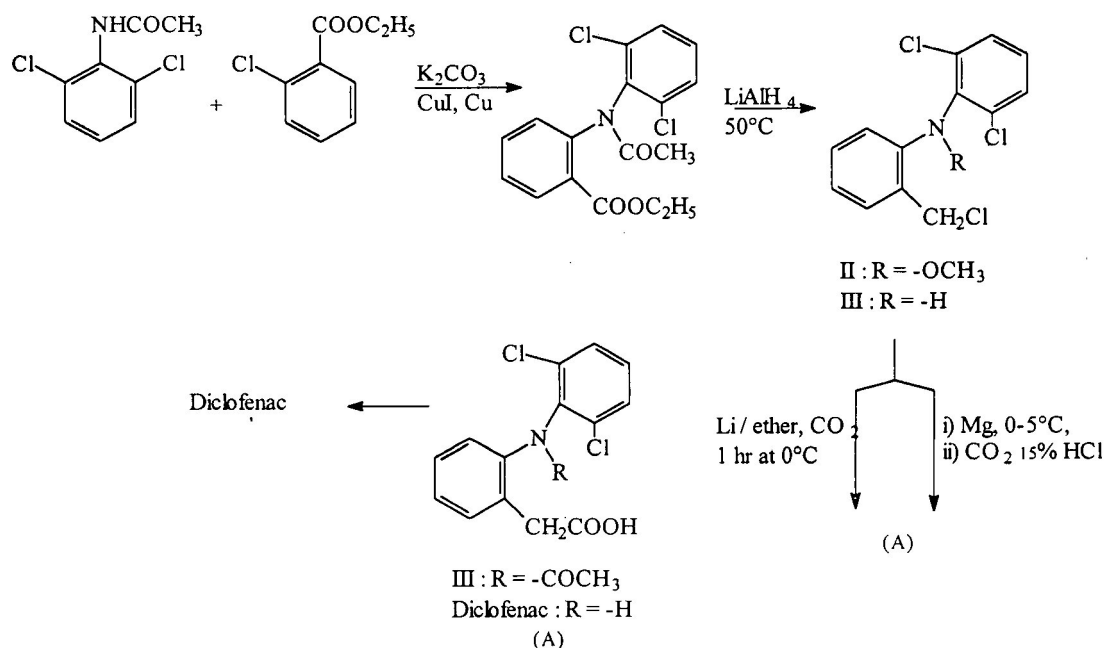


Method 16 :

2,6-dichloroacetanilide and ethyl 2-chlorobenzoate were condensed in presence of K_2CO_3 , at high temp. to give N-(2,6-dichlorophenyl)-N-(o-ethylbenzoate)acetamide(II). Lithium was added to (II) in ether over 1hr. at 0°C , and dry ice added to the mixture to give (III). (III) was refluxed with 10% KOH-ethanol to give Diclofenac¹⁴¹.

In a similar method, 2-(2,6-dichloroanilino)-benzylbromide(IV) in tetrahydrofuran was treated with Mg under nitrogen atmosphere. The mixture was refluxed for 30 min. and cooled to 0°C to 5°C . To this, solid carbon

dioxide, under nitrogen was added and the mixture stirred for 1hr. On treatment with 15% HCl, Diclofenac was obtained¹⁴².



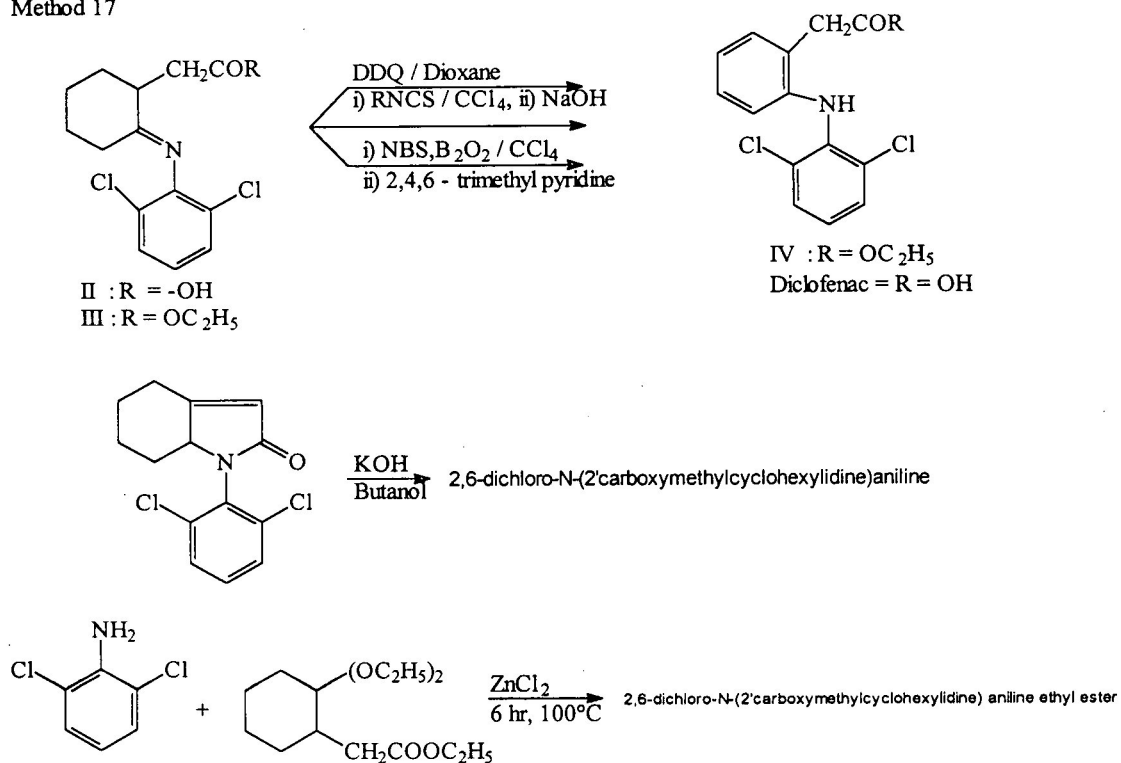
Method 17 :

2,6- dichloro-N-(2'-carboxymethylcyclohexylidene) aniline(II) or its ethyl ester(III) on dehydrogenation gives Diclofenac. In one method, (II) was dehydrogenated with refluxing with DDQ in dioxane¹⁴³. In another, (II) was chlorinated by N-chlorosuccinamide in carbon tetrachloride to get crude dichloro derivative of (II), which was left for 2hr. at 40-50°C in vacuume, treated with 1N NaOH and then treated with HCl to P^H=6 to give Diclofenac¹⁴⁴.

(III) was refluxed with N-bromosuccinamide and dibenzoylperoxide in CCl₄ and then heated with 2,4,6-trimethylpyridine at 150-170°C to give (IV). (IV) was hydrolysed with NaOH-ethanol to give Diclofenac¹⁴⁵.

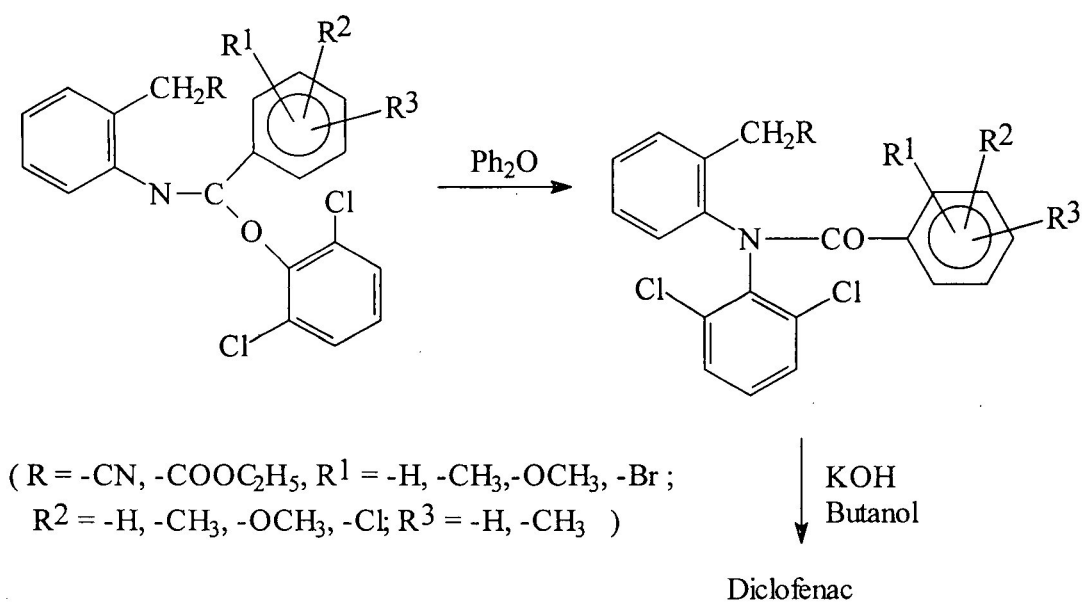
(II) was prepared by refluxing (I) with KOH in butanol for 1hr.¹⁴⁶ (III) was prepared by heating ethyl cyclohexane-2-acetate-diethylacetal with 2,6-dichloroaniline and zinc chloride for 14hr. at 100°C¹⁴⁵.

Method 17



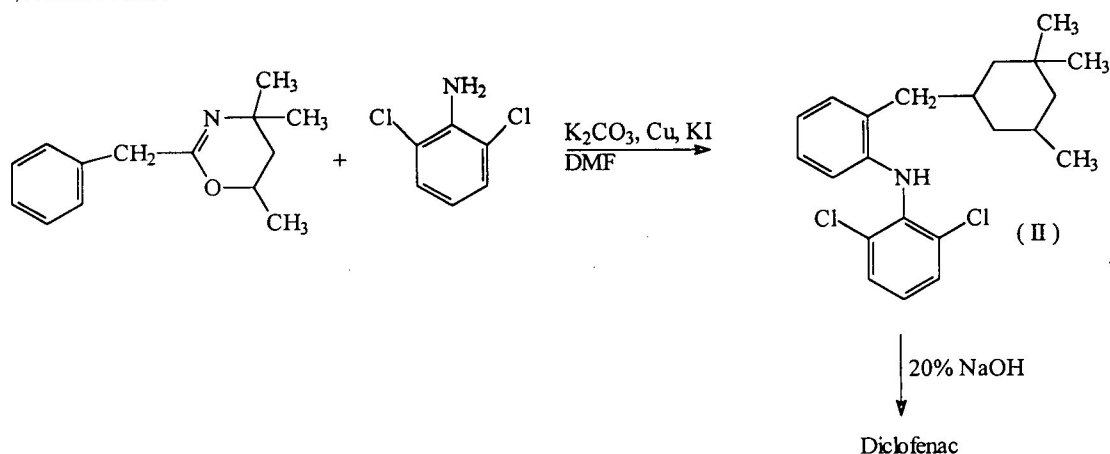
Method 18¹⁴⁷ :

Chapman rearrangement of (I) in diphenyl oxide was carried out to give (II) which was hydrolysed in KOH-butanol to give Diclofenac.



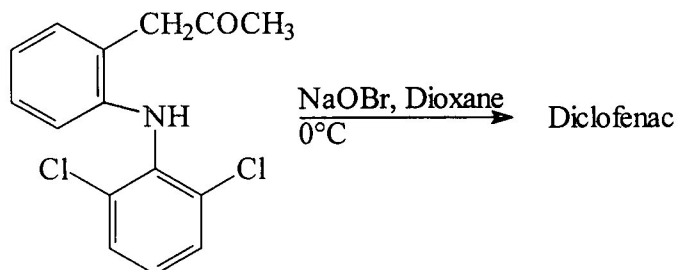
Method 19¹⁴⁸ :

A mixture of 2,6-dichloroaniline, 2-(2-bromobenzyl)-5,6-dihydro-1,3-oxazine(I), K_2CO_3 , CuBr, and KI in DMF was kept for 30min. at 140-160°C to give 50% (II). Refluxing (II) in cellosolve with 20% aqueous NaOH gave 74.3% Diclofenac.



Method 20¹⁴⁹ :

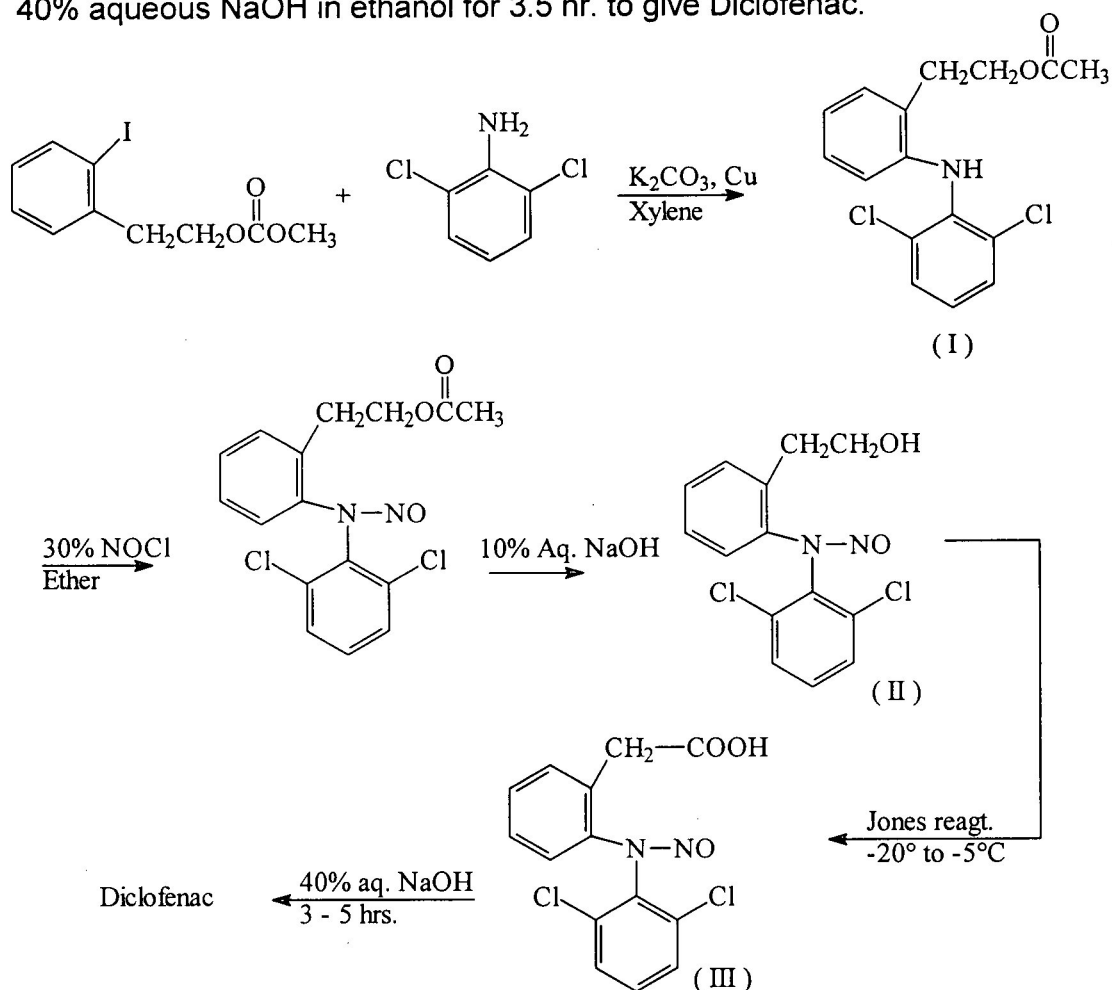
o-(2,6-dichloroanilino)phenylacetone(I) in aqueous dioxane was treated at 0°C with NaBr prepared from 10.5g bromine and 10.5g NaOH, and kept at 0°C for 4h. to give Diclofenac.



Method 21¹⁵⁰ :

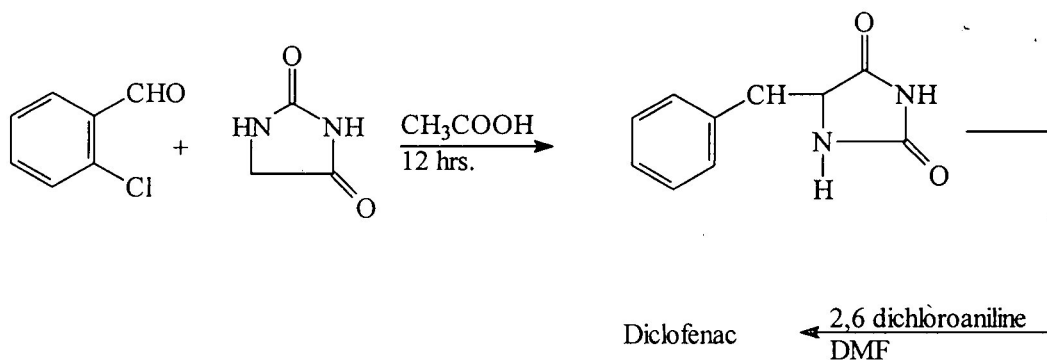
A mixture of O-iodophenylethyl acetate, 2,6-dichloroaniline, Cu, and K_2CO_3 in xylene was refluxed for 70 hr. to give 9% of o-(2,6-dichloroanilino)-phenylethylacetate(I). To a mixture of (I) and triethylamine in ether was added 30% NOCl-ether at 0°C to give o-(N-nitroso-2,6 dichloroanilino)-phenylacetate, which was refluxed in 10% aqueous NaOH (in methanol) to give O-(N-nitroso-2,6-dichloroanilino) phenethylacetate. This was refluxed in methanol to give O-(N-nitroso-2,6-dichloroanilino) phenethyl alcohol(II). Jones reagent and (II) in acetone were stirred for 2 hr. at -20° to -5°C to give 52% of

o-(N-nitroso-2,6-dichloroanilino)phenylacetic acid(III), which was refluxed with 40% aqueous NaOH in ethanol for 3.5 hr. to give Diclofenac.



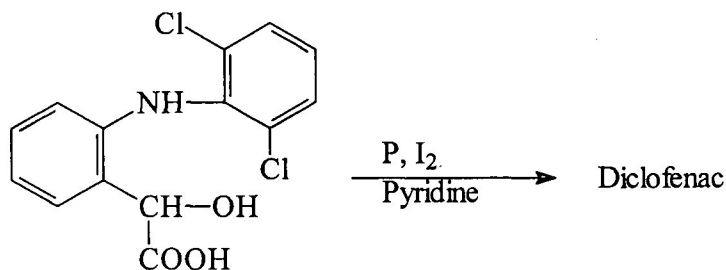
Method 22¹⁵¹:

o-chlorobenzaldehyde was refluxed with hydantoin in acetic acid for 12 hr. to give 70%(II), which was treated with 2,6-dichloroaniline in DMF for 30 hr. at 140-160°C, in the presence of K₂CO₃ and Cu to give Diclofenac.



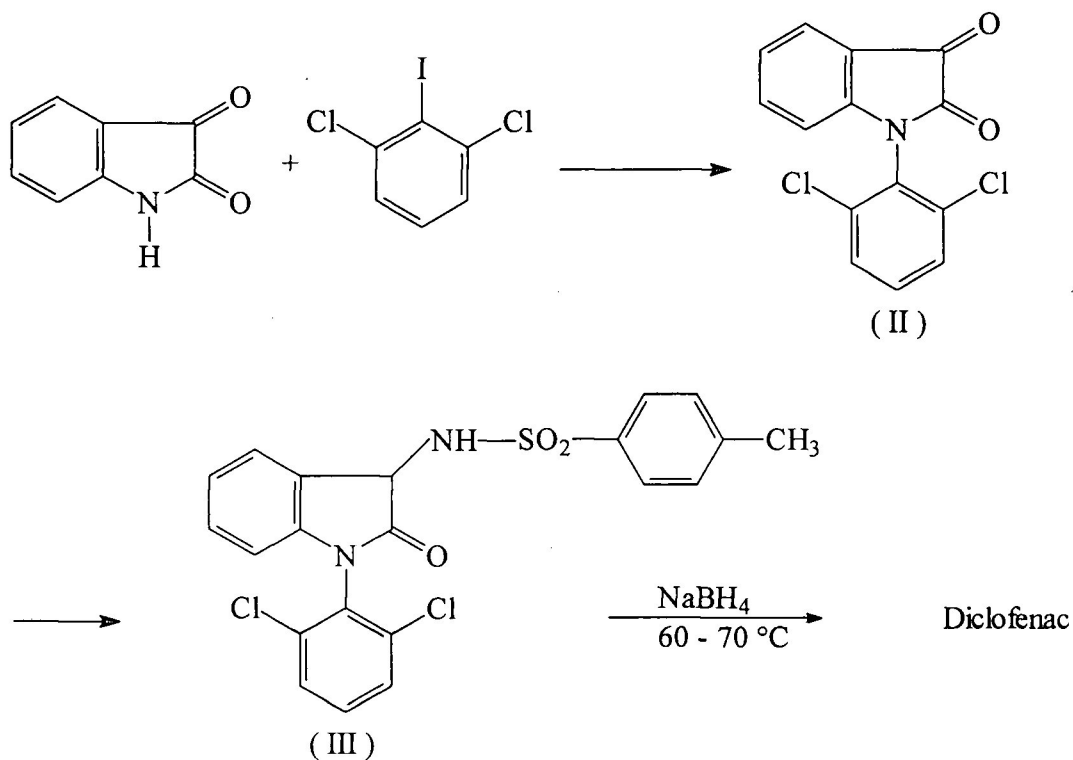
Method 23¹⁵² :

A mixture of phosphorous and iodine in carbon disulphide was stirred for 10 min. at room temp., o-(2,6-dichloroanilino)- α -hydroxyphenylacetic acid(I) was taken in benzene and pyridine, and the whole mixture stirred for 4hr. at room temp. to give 59% diclofenac.



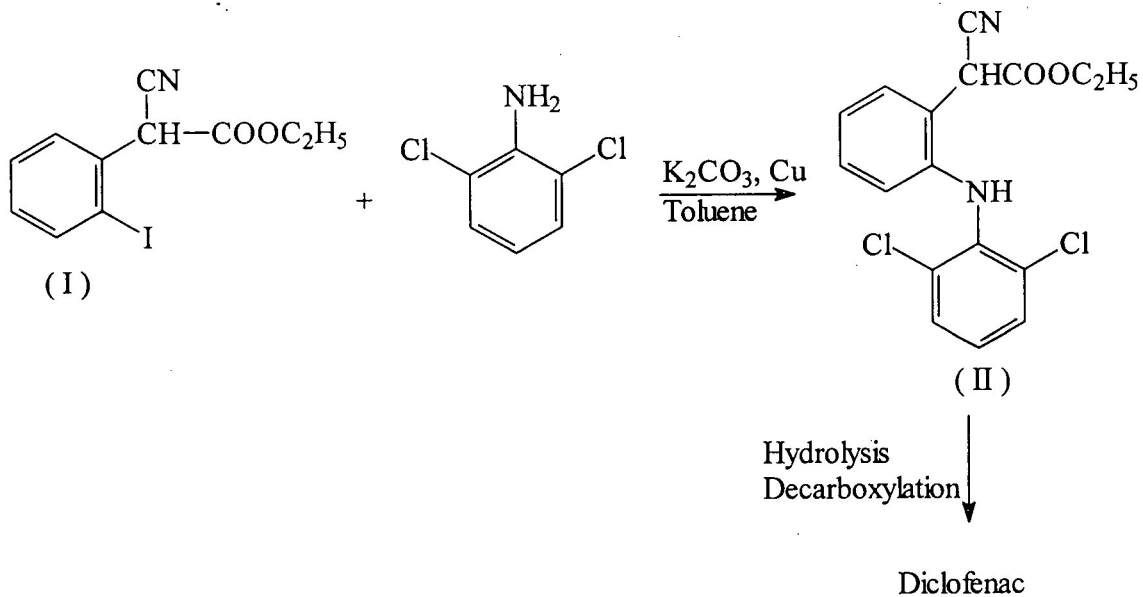
Method 24¹⁵³ :

Isatin(I) was reacted with 2,6-dichloriodobenzene to give N-(2,6-dichlorophenyl)isatin(II), which is condensed with p-toluene sulfonylhydrazide to yield(III). (III) was treated with sodium borohydride at 60-70°C to give Diclofenac.



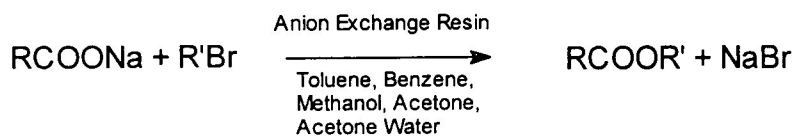
Method 25¹⁵⁴ :

A mixture of o-iodo- α -cyanophenyl acetate(I), 2,6-dichloroanilino, K_2CO_3 and Cu, in toluene gave(II). (II) on hydrolysis and decarboxylation gave Diclofenac.

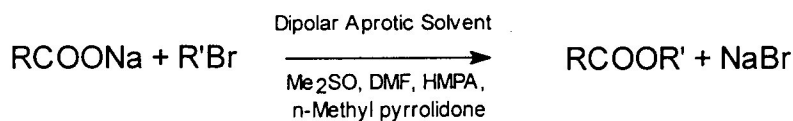


ESTERIFICATION REACTIONS REQUIRED FOR SYNTHESIS OF ACECLOFENAC

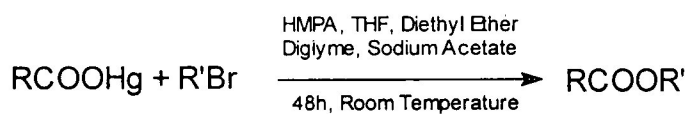
Method 1¹⁵⁵:



Method 2¹⁵⁶:



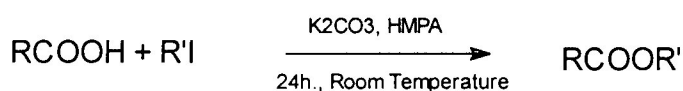
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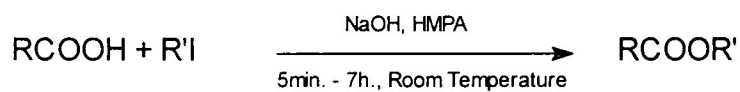
Method 4¹⁵⁸:



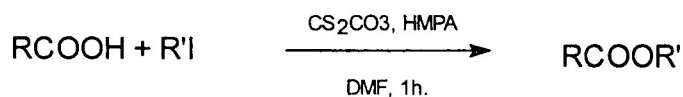
Method 5¹⁵⁹:



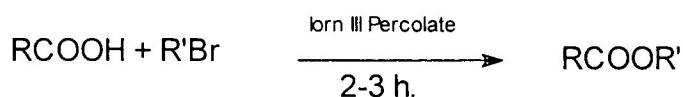
Method 6¹⁵⁹:



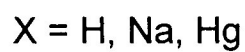
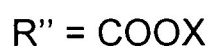
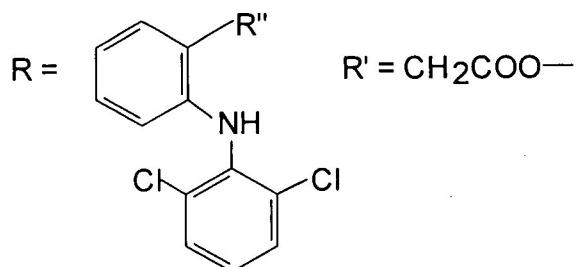
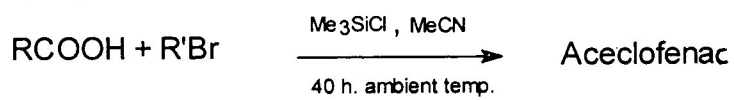
Method 7¹⁵⁹:



Method 8¹⁶⁰:



Method 8¹⁶¹:



Experimental

EXPERIMENTAL : DRAWBACKS OF KNOWN PROCEDURES

O-amino ketones

Though several methods are available for the synthesis of 2-amino substituted benzophenones, they have their own limitations. The classical method of preparation of O-aminoketones requires hazardous solvent extraction procedure for the purpose of isolation of product. Hence, method 1 and 2 are not feasible. Drawback of method 3 is that the yield of the title O-aminoketone is as low as 20%. Method 4, which involves protection of the amino group by tosylation, followed by subsequent preparation of acid chloride and then acylation, does not appeal as it involves a number of steps with the yields dropping at each step. Method 5 fails to give good yields apart from making use of a poisonous gas like phosgene.

Method 6, which involves photolysis of the substituted benzisoxazole in concentrated hydrochloric acid, gave a mixture of 2-amino substituted benzophenones. Thionyl chloride catalyzed cleavage of 2,1-benzisoxazoles leads to introduction of an additional Cl atom into the benzisoxazole. Similarly, methods 8 and 9 are not promising.

Method 10, although giving good yields of the title o-aminoketone is not economical as iodotrimethylsilane or chlorotrimethylsilane is very costly.

Method 11, involves reductive cleavage of benzisoxazole to give the title o-aminoketones. Reduction of the benzisoxazole using ferrous sulphate, hydrochloric acid in isopropyl alcohol poses the problems like low yield and difficulty in isolation of product from the reaction mixture. Reduction using iron-hydrochloric acid in methanol or ethanol also gives low yields.

Attention was, therefore, focussed on routes not involving hazardous chemicals and reactions, and at the same time provided a clean work up and high yields of the title ketones.

Diclofenac sodium

From the literature reports, it is quiet clear that many routes are available for the synthesis of diclofenac sodium. The reported methods have been evaluated stepwise as follows :

Method 1 :

This method appears to be the "best" method for synthesis since it starts from a very basic stage. The raw materials are readily available, minimum number of steps are involved, reactions are feasible on a large scale and good yields are possible.

Method 2 :

Although this route is also a good method but it involves an additional step for reducing 1-(2,6-dichlorophenyl) indole-2,3-dione(III).

Method 3 :

This method involves an additional step of reducing 2-(2,6-dichloroanilino) phenyl glyoxalic acid(I).

Method 4 :

Even though the initial reaction condition is favorable, one should note that the starting material 2,6-dichloro-4-nitro iodobenzene is not available cheaply. Also it involves reduction with hydrogen iodide and phosphorous, which is not a feasible method industrially. It also involves an additional step of removal of amino group.

Method 5 :

This method involves use of N-chlorosuccinimide which is not feasible on industrial scale. Also, it involves an additional step of reduction with Raney Nickel. This increases the cost of the process.

Method 6 :

This method involves only one step but gives low yields. The starting drug intermediate o-halo or o-amino phenyl acetic acid is not available cheaply.

Use of a strong base like sodium hydride makes the process less feasible and uneconomical.

Method 7 :

The starting drug intermediate N,N-diethyl-2-aminophenylacetamide and 2,6-dichloriodobenzene are not available so commonly.

Method 8 :

This method involves a large number of steps and the Willgerodt-Kindler reaction in the latter step is not a clean reaction. The yields are usually low in such reaction.

Method 9 :

This method involves use of Magnesium and Lithium compounds which are extremely dangerous to handle on plant scale and the process becomes uneconomical for future work.

Method 10 :

This method involves the use of diazomethane which is extremely poisonous and difficult to handle on plant scale, due to its explosive property.

Method 11 :

This method involves more number of steps and also, the use of LiAlH_4 (t-butoxide)₃ makes the process uneconomical for the manufacture.

Method 12, 13, 15 :

More number of steps, costly starting materials, use of costly reagents like triphenylphosphine, titanium salts, etc. make these methods less appealing for further exploitation.

Method 14 :

Starting material O-(2,6-dichloroanilino) benzaldehyde is itself difficult to prepare. Even if the starting material is obtained, the steps involved in the entire process make it a costly affair for industrial use.

Method 16 :

It involves the use of use of LiAlH_4 and lithium which are difficult to handle on a plant scale and hence, the process becomes uneconomical.

Method 17 :

This method involves dehydrogenation of cyclohexane ring to benzene using costly reagents such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone or N-chlorosuccinamide and dibenzoylperoxide or N-bromosuccinamide and dibenzoylperoxide. Hence, this route is not feasible on plant scale and also uneconomical.

Method 18, 21 :

The starting product is difficult to synthesize economically and subsequent steps do not give good yields and the methods are not profitable.

Method 19 :

This method involves costly starting material. Also low yields make the route uneconomical.

Method 20 :

The starting material O-(2,6-dichloroanilino)phenylacetone is difficult to synthesize, making the process uneconomical.

Method 22 :

Use of hydantoin and low yields make the process uneconomical.

Method 23 :

Starting material, O-(2,6-dichloroanilino)hydroxy phenylacetic acid(I) is difficult to synthesize economically. Use of phosphorous and iodine as reducing mixture makes the process unsuitable for large scale manufacture.

Method 24, 25 :

Starting materials are difficult to synthesize economically. Also, the low yields make the method uneconomical.

Aceclofenac :

In the esterification reaction required for the synthesis of Aceclofenac, the methods listed in literature utilize

- 1) Solvents which are costly and difficult to procure.
- 2) Reagents used in most methods like, iron III percolate, anion exchange resin, methyl cyanide etc. are expensive, harmful and complex.
- 3) The yield of the reaction is less and poses problem during isolation of the final product.

Hence, it becomes difficult to carry out the reaction under such conditions.

EXPERIMENTAL : PRESENT WORK

Part I :

Synthesis of 2-amino 2'-fluoro 5-chloro benzophenone

Synthesis involves two steps :

Step I

Preparation of 2-fluorobenzoyl chloride

In a dry 100ml round bottomed flask equipped with water condenser and a guard tube was placed 5g (0.03M) of 2-fluorobenzoic acid. To this was added 7.25g (4.45ml) of freshly distilled thionyl chloride and two drops of DMF as a catalyst. The whole mixture was refluxed in an oil bath at 85°C for 4-5h. Excess thionyl chloride was removed by distillation. The remaining liquid was subjected to distillation under reduced pressure and pure 2-fluorobenzoyl chloride was collected at 48-52°C / 60mm.

Yield = 3ml, 74%.

B.P. (Lit.) = 50°C / 60mm.

Step II

Condensation of 2-fluorobenzoyl chloride with 4-chloroaniline

In a 100ml three-necked round bottomed flask equipped with mechanical stirrer, air condenser, with guard tube and stopper, was placed 5.28g. (4ml, 0.033M) of 2-fluorobenzoyl chloride. It was heated upto 130-140°C. At this temperature, 1.6g. (0.013M) of 4-chloroaniline was added in portions with vigorous stirring over a period of 30 min. The temperature was increased upto 180-200°C. At this temperature, anhydrous zinc chloride 2.4g. (0.017M) was added in portions. The addition took 30 min. The temperature was increased upto 230°C and maintained for 3h. After 3h., it was cooled down to 120°C. To this was added 50ml of boiling water, the whole reaction mixture was stirred for 15-20 min. and the contents were poured into a beaker. The supernatant liquid was removed and the residue was again placed in a three necked flask. To this added 50 ml boiling water. Air condenser was replaced by water condenser. The reaction mixture was again refluxed for 15-20 min. at 120°C. Again water was removed and the residue was treated with boiling water. After three such treatments with boiling water, residue was treated with 5%

solution of sodium hydroxide. It was washed with cold water and again placed in three necked flask. To this, 12.5ml of 70% sulfuric acid was added. The mixture was refluxed at 130⁰-140⁰C for forty minutes. It was allowed to cool down to room temperature and was poured in crushed ice. A slightly sticky solid separated out. The water was decanted and solid was again treated with crushed ice. The solid became granular. Again water was decanted and solid was treated with solid sodium bicarbonate and 5% sodium hydroxide. It was decanted and washed with cold water. The solid was separated by filtration and recrystallised from methanol.

Yield = 2.2g, 66.8%.

M.P. = 92⁰-93⁰C.

M.P.(Lit.) = 94⁰-95⁰C

Elemental analysis of C₁₃H₉NCIFNO

	C%	H%	N%
Calculated	62.5	3.6	5.61
Found	62.01	3.45	5.68

Spectral Analysis

IR (KBr)

Wavenumber (cm ⁻¹)	Assignment
3435, 3328	NH Stretching(Aromatic amine)
1619	C=O stretching
1156	C-F stretching
704	C-Cl stretching

PMR (CDCl₃ – TMS) δ

7.4 – 7.8	m, 7H, Ar-H
6.8	d, 7H, Ar-H
6.4	s, 2H, NH ₂

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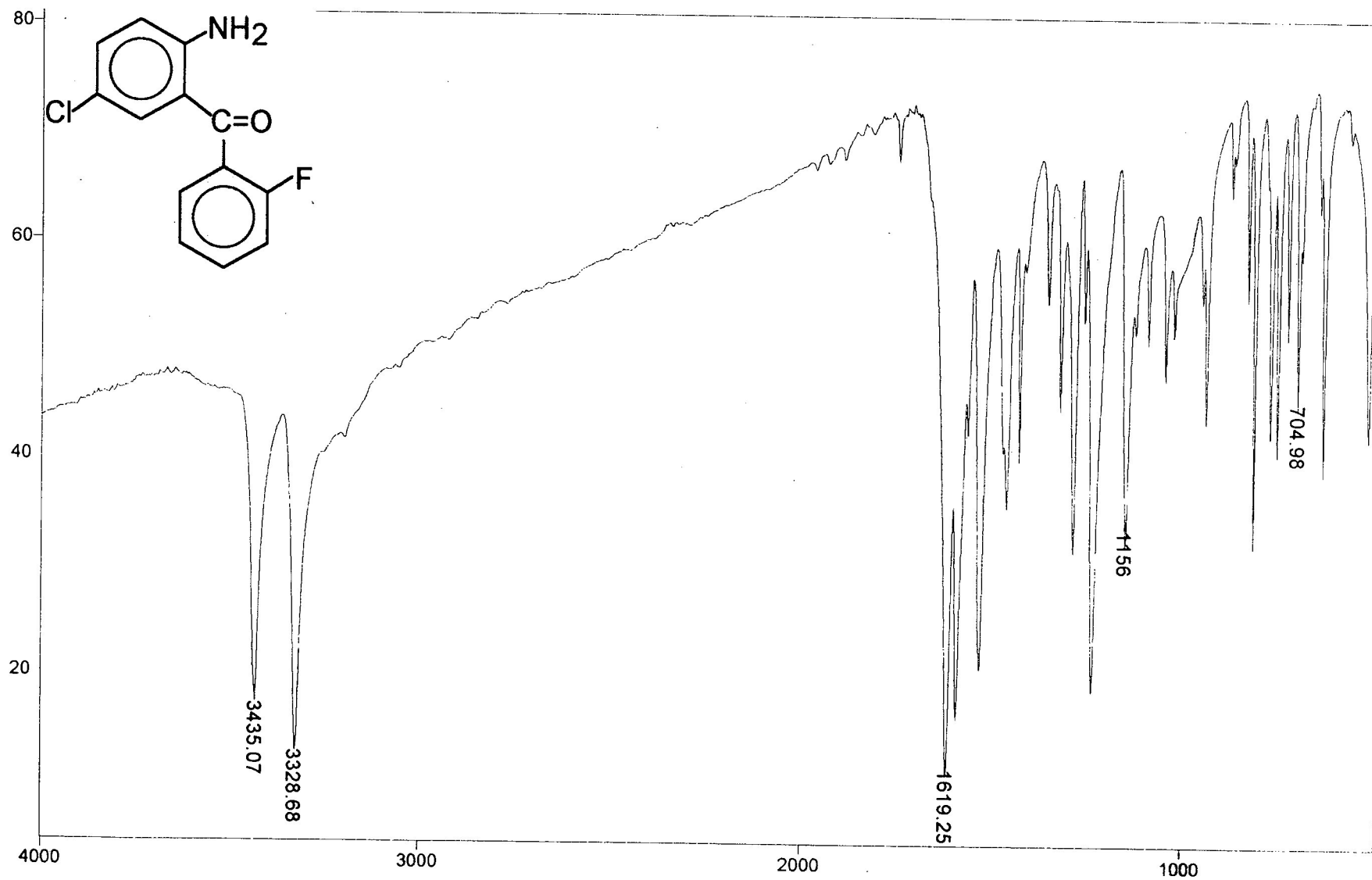
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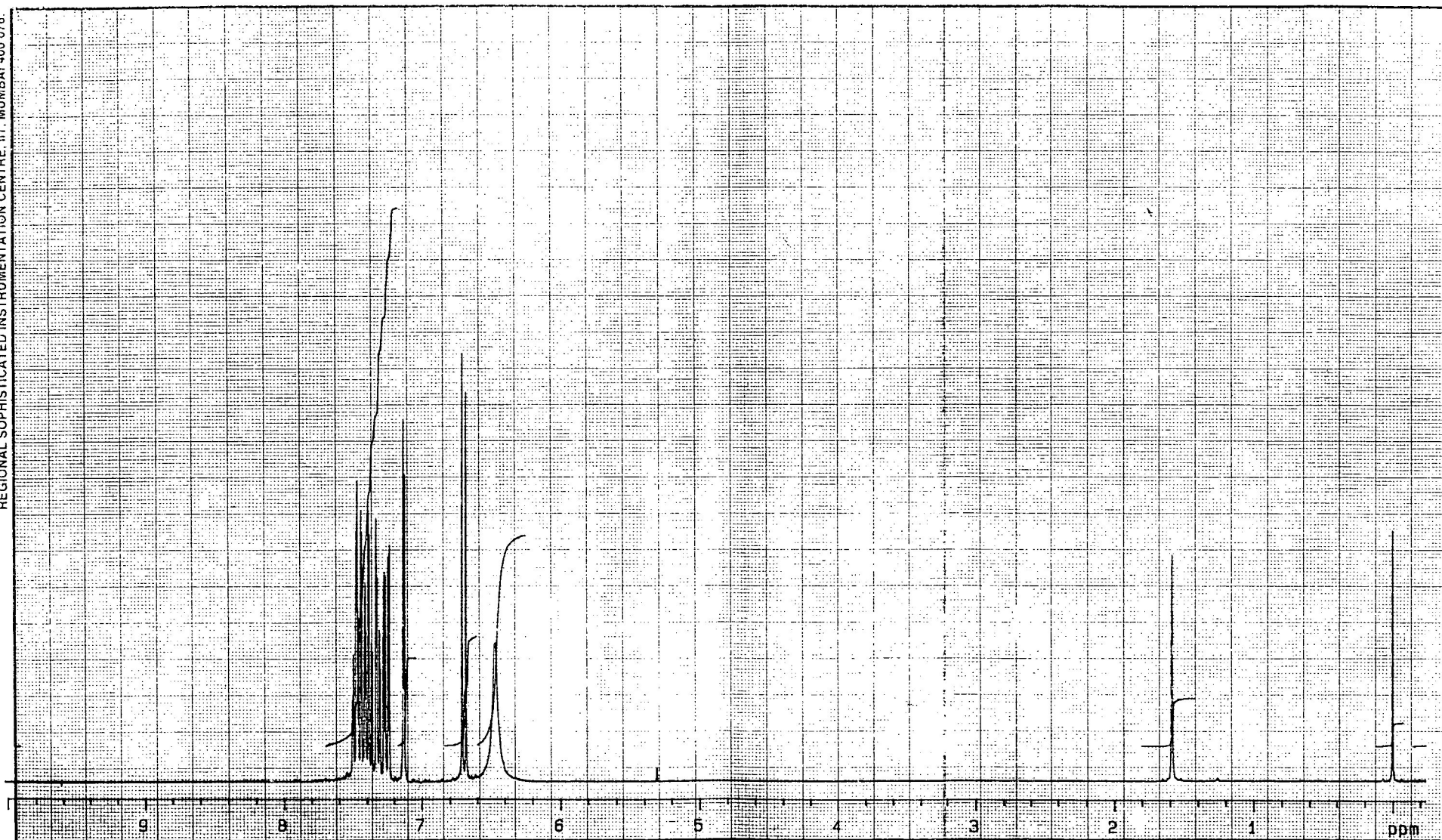
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Res=4 cm-1

Apod= Cosine

Zero Filling= 1 x





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 Modulation Mode c Freq. 200 Hz
 Pulse Width not used μ sec Power Mode not used

PLOT/PROCESSING
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 Solvent CDCl3

Number exp
 File May 28 99
 Date 300
 VPRO

Part II :

Synthesis of 2-amino 2'-chloro 5-nitro benzophenone

Synthesis involves two steps

Step I

Preparation of 2-chlorobenzoyl chloride

In a dry 100ml round bottomed flask, equipped with water condenser and guard tube was placed 5g. (0.032M) of 2-chlorobenzoic acid. To this was added 7.25g (4.45ml) freshly distilled thionyl chloride and two drops of DMF as catalyst. The whole mixture was refluxed in an oil bath at 80-85°C for 4-5h. The excess of thionyl chloride was removed under reduced pressure along with benzene. The remaining liquid was subjected to distillation and pure 2-chlorobenzoyl chloride was collected at 137-139°C / 60mm.

Yield = 4.2g., (3ml), 75.13%.

B.P. (Lit.) = 137-139°C / 60mm.

Step II

Condensation of 2-chlorobenzoyl chloride with 4-nitroaniline

In a 100ml three-necked round bottomed flask equipped with a mechanical stirrer, air condenser, guard tube and stopper, was placed 23.49g (17ml, 0.13M) of 2-chlorobenzoyl chloride. It was heated upto 130-140°C on an oil bath. At this temperature, 8.54g. (0.06M) of 4-nitroaniline was added in portions with vigorous stirring, over a period of 30 min. The temperature was increased upto 180-200°C. At this temperature anhydrous zinc chloride 121g. (0.088M) was added in portions. The addition took 30 min. The temperature was increased upto 230°C and maintained for 3h. It was cooled to 120°C. To this, 50ml of boiling water was added and the whole reaction mixture was stirred for 15-20 min. The contents were poured into a beaker. The supernatant liquid was removed and the residue was again placed in three necked flask. To this was added 50ml of boiling water. Air condenser was replaced by water condenser. The reaction mixture was again refluxed for 15-20 min. at 120°C. Again water was removed and residue was treated with boiling water. After three such treatments with boiling water, residue was treated with 5% sodium hydroxide solution. Solid was washed with cold water and again placed in three necked flask. To this was added a mixture of 13.8ml

water, 18.9ml acetic acid and 24.5ml conc. sulfuric acid. The mixture was refluxed at 133⁰-140⁰C for 4h. It was then kept overnight. It was then poured in crushed ice and a sticky solid was separated out. The water was decanted and solid was again treated with crushed ice. The solid became granular. Again water was decanted and solid was treated with 5% NaOH solution. It was decanted and washed with cold water. The solid was separated by filtration and recrystallised from methanol.

Yield = 9.8g, 58%.

M.P. = 122⁰C to 123⁰C.

M.P. (Lit.) = 118-121⁰C.

Elemental analysis of C₁₃H₉ClN₂O₃

	C%	H%	N%
Calculated	56.4	3.25	10.12
Found	56.7	3.4	10.11

Spectral Analysis

IR (KBr)

Wavenumber (cm ⁻¹)	Assignment
3447, 3334	NH Stretching(Aromatic amine)
1644	C=O stretching
1306	C-N stretching
1481	NH stretching (Aromatic)
704	C-Cl stretching

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Mode= 2 (Mid-IR)

5/13/99 6:42 PM

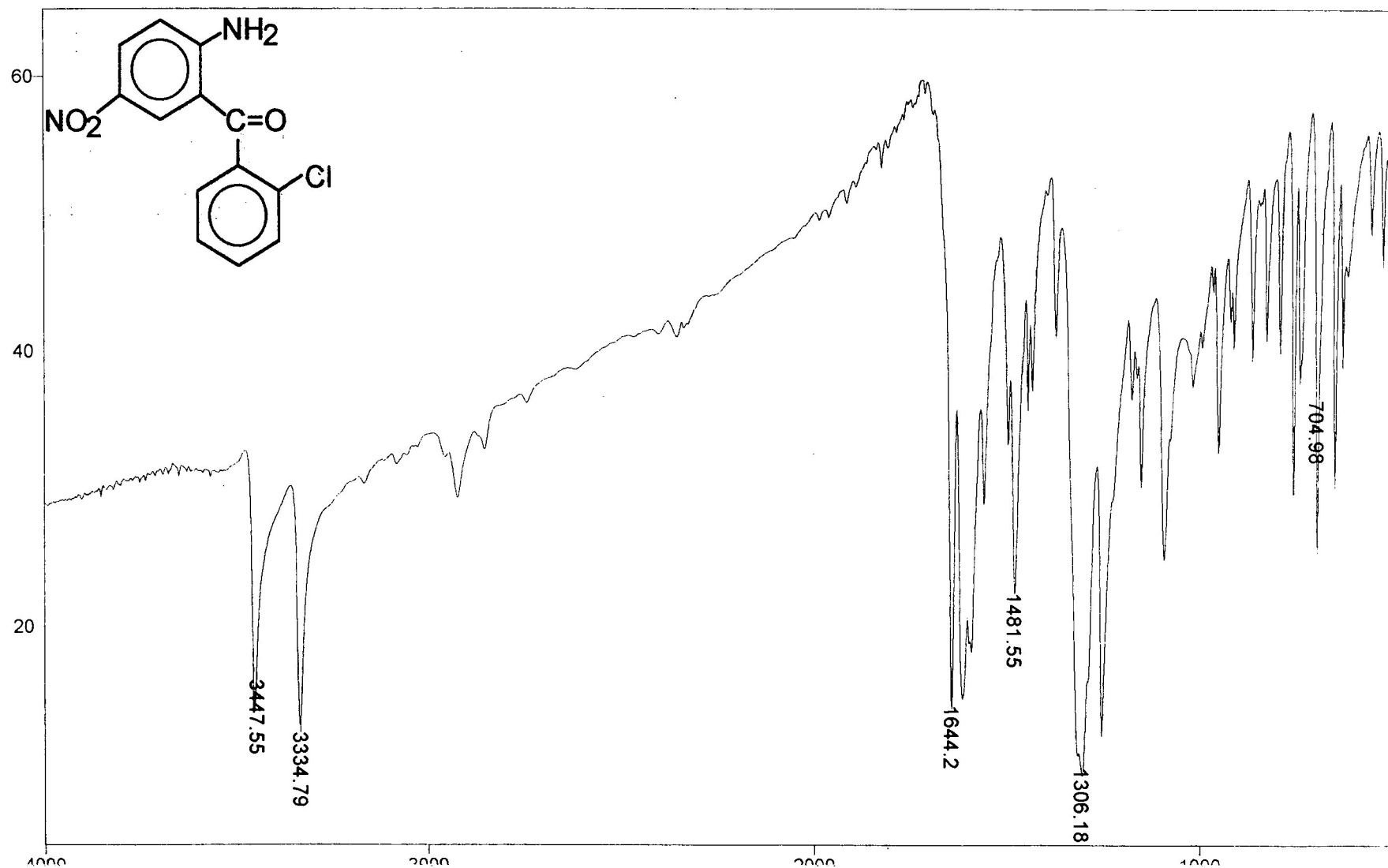
Sample Description: 2-amino 2'chloro 5-nitro benzophenone

Scans= 10 Slow

Res=4 cm-1

Apod= Cosine

Zero Filling= 1 x



Part III :

Synthesis of 2-chloro-1(4-fluorobenzyl)benzimidazole

Synthesis involves following steps

Step I :

Synthesis of 2-mercapto benzimidazole :

To potassium hydroxide (5.6g, 0.1M) was added 150ml ethanol and 30ml water. The mixture was warmed on water bath till all the solid goes into solution. To this cold solution was added carbon disulfide (13.5g, 11ml, 0.17M) with stirring this resulted in the formation of potassium ethyl xanthate.

In a 250ml three-necked round bottomed flask equipped with a dropping funnel and a reflux condenser was placed O-phenylenediamine (1.2g, 0.1M) in 200ml ethanol. To this, the above potassium ethyl xanthate solution was added dropwise. The mixture was further refluxed for 6hr. until evolution of hydrogen sulfide gas ceases. The reaction mixture was cooled and then concentrated under vacuum to remove most of the ethanol. The oil obtained was diluted with water and then neutralized with dilute HCl. The solid separated out was filtered, washed with water and dried. It was then recrystallised from ethanol.

Yield = 13.3g, 80%.

M.P. = 302⁰-303⁰C.

M.P.(Lit.) = 301⁰-305⁰C.

Step II :

Preparation of 2-chlorobenzimidazole :

In a 100ml three-necked round-bottomed flask equipped with an air condenser, 2-mercaptobenzimidazole (2g, 0.01M) was taken in chloroform:water (2:1) and cooled to 5⁰C. A slow stream of chlorine gas was bubbled through the solution for 1hr., while maintaining the temp. below 10⁰C. At the end of this, the reaction mixture was transferred to evaporating dish to expel excess chlorine. Evaporation of solvent afforded a sticky mass. Passage of the material through silica gel column and elution with chloroform gave the purified product.

Yield = 0.9g, 45.7%.

M.P. = 180⁰-182⁰C.

M.P.(Lit.) = 180⁰C

Step III :

Addition of 4-fluorobenzyl chloride to 2-chlorobenzimidazole :

In a 50ml round-bottomed flask was taken a mixture of 6g (0.039M) of 2-chlorobenzimidazole and 0.7ml (0.01M) of triethylamine in 20ml dioxane and 2ml DMF (9:1) and was stirred at 60⁰C for 1hr. Then 8.4g (0.058M) of 4-fluorobenzyl chloride was then added. This was refluxed for 4h. After the completion of the reaction, the mixture was poured into 700ml cold water. The precipitate formed was filtered and recrystallised from methanol.

Yield = 6.0g, 59.2%.

M.P. = 74⁰-75⁰C.

M.P.(Lit.) = 75⁰-76⁰C

Elemental analysis of C₁₄H₁₀ClN₂

	C%	H%	N%
Calculated	64.49	3.83	10.74
Found	64.97	3.76	10.94

Spectral Analysis

IR (KBr)

Wavenumber (cm ⁻¹)	Assignment
2952,3040	CH ₂ , alkyl group Stretching
1600	C=N stretching of heterocyclic group
1506	C=C skeletal vibration of aromatic ring
1218	C-F stretching
665	C-Cl stretching

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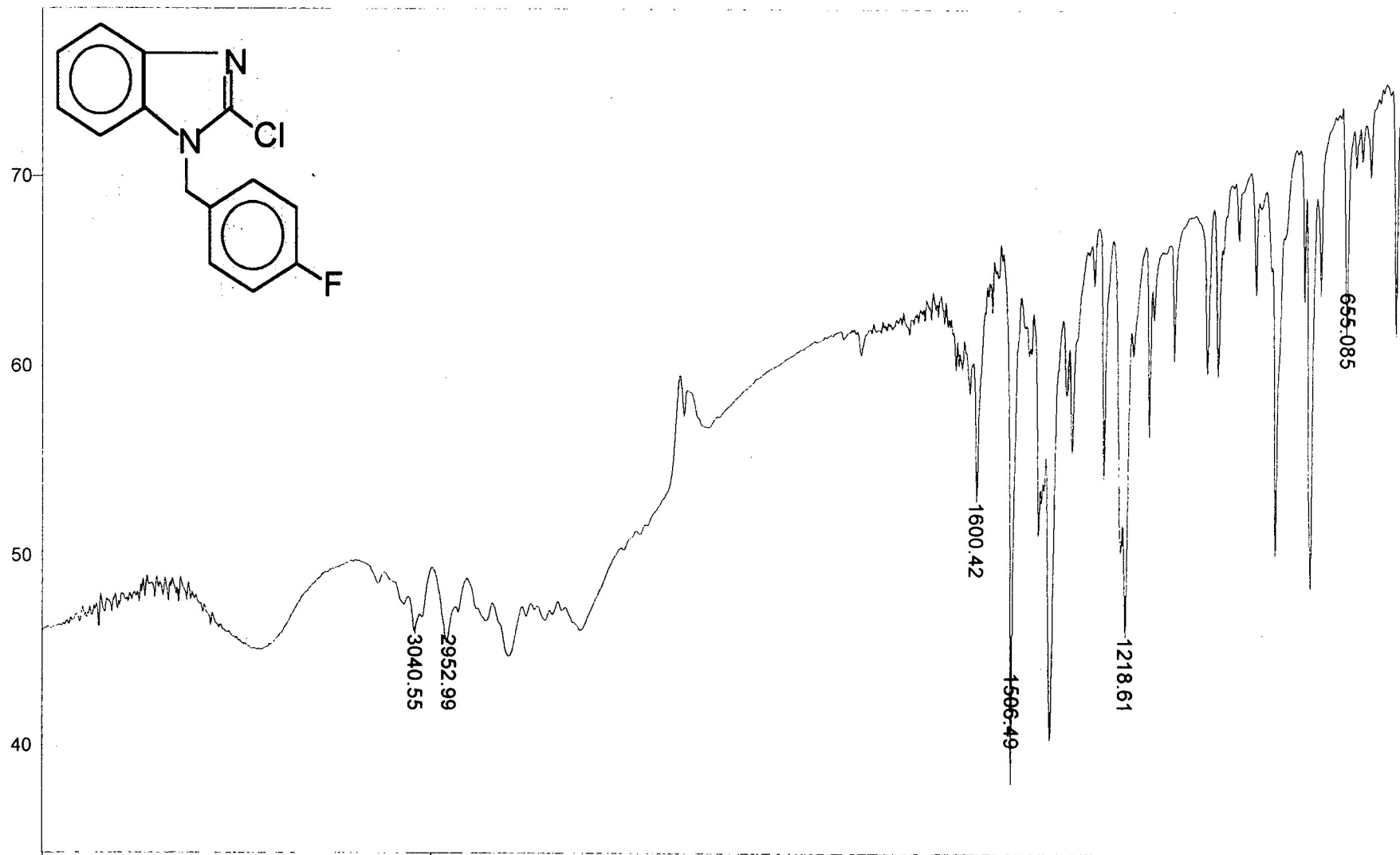
Sample Description: fbcbi

Scans= 10 Slow

Res=4 cm-1

Apod= Cosine

Zero Filling= 1 x



Part IV :

Synthesis of Aceclofenac :

Diclofenac sodium is an intermediate required for the synthesis of Aceclofenac. The present work of synthesis of Diclofenac sodium is based on the route given by method 1. The various steps involved are :

Step I :

Preparation of 2,6-dichloroacetanilide :

In a 500ml round-bottomed flask equipped with a reflux condenser, 49g (0.3M) of 2,6-dichloroaniline was placed. To this, 60ml of glacial acetic acid was added. The mixture was refluxed for six hours, and the hot liquid was poured in a thin stream into a 2-liter beaker containing 500g of crushed ice whilst stirring continually. The crude product was filtered at pump and washed with cold water, drained well and dried upon filter paper in the air. The crude product was recrystallised from 25% aqueous acetic acid.

Yield = 80%.

M.P. = 174⁰-175⁰C.

M.P. (Lit.) = 175⁰C.

Step II :

Preparation of N-(2,6-dichlorophenyl)amine :

In a two liter three-necked round bottomed flask equipped with a mechanical stirrer and Dean and Stark apparatus, was taken 400g of bromobenzene, 41g (0.2M) of 2,6-dichloroacetanilide, 1g copper, 1g cupric oxide, 1g potassium iodide, and 40g anhydrous potassium carbonate were added while stirring. The mixture was refluxed for 56hr with continuous removal of water. After cooling, the reaction mixture was filtered out at pump and subjected to steam distillation to recover excess bromobenzene. The product, which was not steam volatile, separated out as a solid on cooling the flask, and was filtered out.

In a one liter two-necked round-bottomed flask equipped with a reflux condenser and a dropping funnel was placed a solution of 40g(0.15M) of N-(2,6-dichlorophenyl)-N-phenylacetamide in 100ml ethanol. The solution was heated under reflux. Through the dropping funnel 50ml conc. hydrochloric

acid was added over a period of 30 minutes. The mixture was refluxed for additional four hours and then diluted with 200ml water. The flask was fitted for downward distillation and about 150ml of distillate was collected. The remaining portion of the mixture was poured into 500ml cold water. The amine separated out as an oil. It was extracted using 2 x 50ml portions of chlorobenzene. The extracts were combined and washed with 2 x 100ml 25% NaHCO_3 solution and then with water. The extracts were concentrated by removing chlorobenzene on rotary evaporator. The crude product obtained was purified from ethanol.

Yield = 30.6 gm, 69.2%.

M.P. = $52^\circ\text{--}53^\circ\text{C}$.

M.P. (Lit.) = $51^\circ\text{--}52^\circ\text{C}$.

Spectral Analysis

IR (KBr)

Wavenumber (cm^{-1})	Assignment
3370	N-H Stretching
1500	N-H bending
690	C-Cl stretching

Step III :

Preparation of N-chloroacetyl derivative :

30.5 gm (0.128 M) of 2,6-dichlorodiphenylamine was taken in a dry 500ml round bottomed flask fitted with a reflux condenser having a calcium chloride guard tube at the open end. The reaction assembly was essentially fitted in a fuming cupboard. 100ml (141.8 gm, 1.39M) of freshly distilled chloroacetyl chloride was added quickly and the mixture was refluxed for two hours. The flask was then fitted for downward distillation and the excess chloroacetyl chloride was recovered. The cooled mixture was washed with 25% NaHCO_3 solution (3 x 100ml). The solution of N-chloroacetyl derivative in toluene was concentrated on rotary evaporator. The crude material obtained was recrystallised from methanol and utilized for the next reaction immediately.

Yield = 14.8gm, 48%.

M.P. = 141⁰-142⁰C.

M.P. (Lit.) = 143⁰-144⁰C.

Step IV :

Preparation of 2,6-dichlorophenyl indolinone

14 gm (0.049M) N-chloroacetyl derivative of 2,6-dichlorodiphenylphenyl amine was taken in a 500ml three-necked round-bottomed flask fitted with a mechanical stirrer, reflux condenser and a thermometer. 14g (0.103M) of anhydrous AlCl₃ was added and the reaction was heated upto 120⁰C, with constant stirring, for three hours. The cooled reaction mixture was poured down slowly with continuous stirring on 500g crushed ice contained in a 1 liter beaker. The organic layer was subjected to steam distillation and chlorobenzene was recovered. The product, which is non-volatile in steam, comes out of solution on cooling. It is filtered out and dried. It is then recrystallised from dilute methanol.

Yield = 9.34 gm, 69%.

M.P. = 125⁰-126⁰C.

M.P. (Lit.) = 126⁰-127⁰C

Spectral Analysis

IR (KBr)

Wavenumber (cm ⁻¹)	Assignment
1732	C=O Stretching
1240	C-N vibration
1171	C-C stretching
670	C-Cl stretching

Step V :

Preparation of Diclofenac Sodium

In a one liter round-bottomed flask equipped with a condenser was taken 15g (0.07M) of 1-(2,6-dichlorophenyl)-2-indolinone. To this, 140ml 1N sodium

hydroxide and 210ml ethanol were added and the mixture was refluxed for 2h. The solvent was removed on rotary evaporator and all the alcohol was recovered. The solution was then diluted with 50ml water and strongly acidified with hydrochloric acid and cooled. Diclofenac precipitated out was filtered at the pump. In a 500ml round bottomed flask fitted with a reflux condenser was taken 10g (0.337M) of Diclofenac. 100ml of dry ethanol and 13.6g accurately weighed sodium hydroxide was added and the solution was refluxed over a water bath for one hour. Solvent was removed on rotary and the sodium salt of Diclofenac separates out in the flask.

Yield = 15.1 gm, 64%.

M.P. = 281⁰-282⁰C.

M.P. (Lit.) = 283⁰-285⁰C

Spectral Analysis

IR (KBr)

Wavenumber (cm ⁻¹)	Assignment
1575,1306	O=C=O carboxylate anion stretching
1506	N-H bending
1281	C-N vibration
749	C-H bending

Step VI :

Preparation of Aceclofenac

A mixture of 2g (0.0062M) diclofenac sodium , 0.52g (0.062M) sodium bicarbonate, 1.72g (0.0124M) bromoacetic acid in 10ml dimethylformamide was taken in 25ml round-bottomed flask equipped with an air condenser. The reaction mixture was stirred magnetically for 5h. at 0-5⁰C. After completion of reaction, the reaction mixture was poured over 50ml ice cold water. A milky solution was obtained, which was then extracted with ethyl acetate. The ethyl acetate extracts were combined and concentrated to obtain a sticky solid. This sticky solid mass was dissolved in benzene and passed through silica gel column and the column was eluted with benzene to give Aceclofenac.

Yield = 1.7g, 74.2%.

M.P. = 153⁰-154⁰C.

M.P. (Lit.) = 150⁰-151⁰C.

Elemental analysis of C₁₆H₁₃Cl₂NO₄

	C%	H%	N%
Calculated	54.23	3.67	3.95
Found	54.2	3.87	4.24

Spectral Analysis

IR (KBr)

Wavenumber (cm ⁻¹)	Assignment
2965	CH ₂ , alkyl group Stretching
1732	COOCH ₂ ester group stretching
1362	COOH stretching
1562	C=C skeletal vibration of aromatic ring
1299	C-N vibration
667	C-Cl stretching

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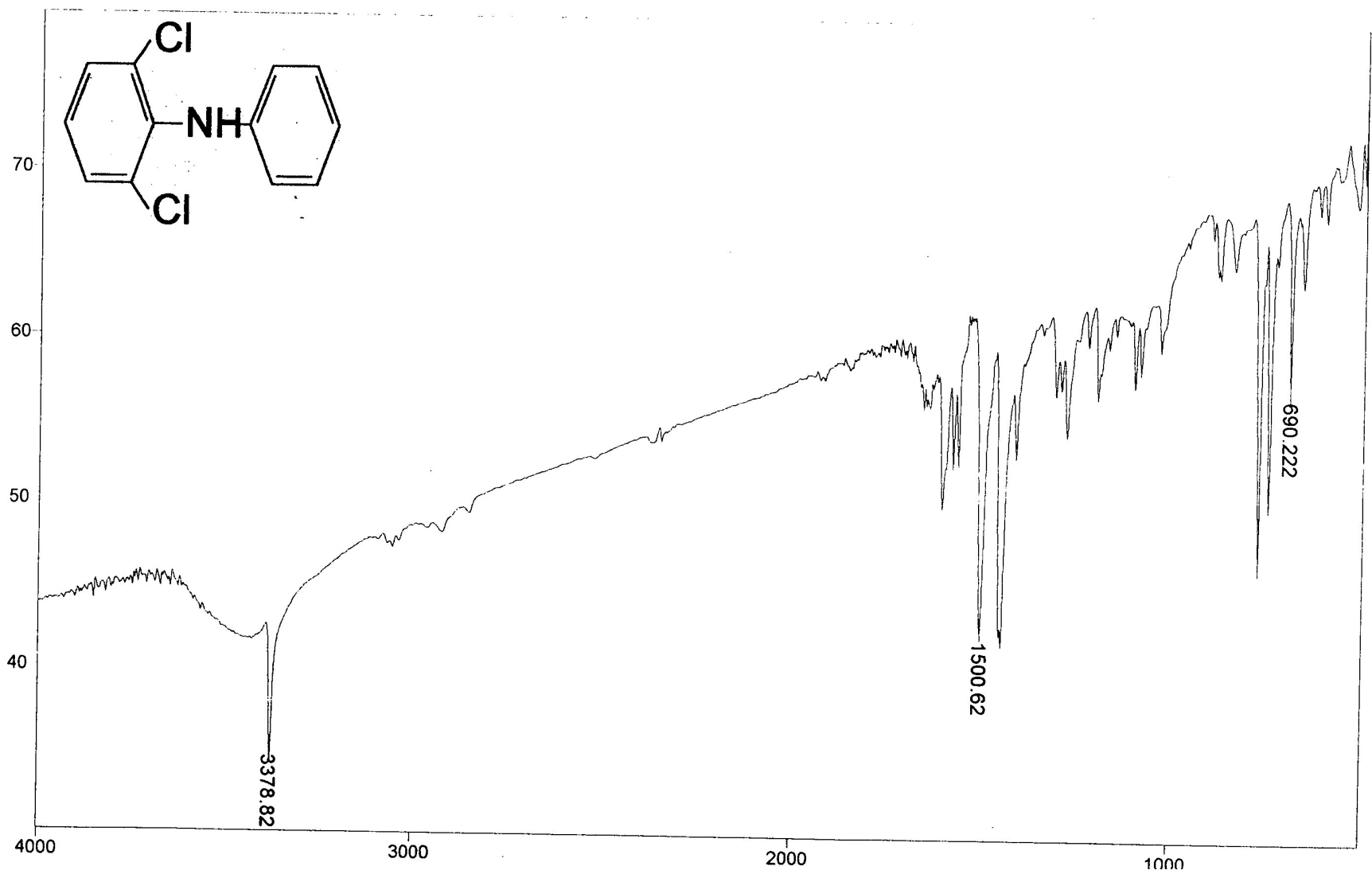
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Scans= 10 Slow

Res=4 cm-1

Apod= Cosine

Zero Filling= 1 x



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Mode= 2 (Mid-IR)

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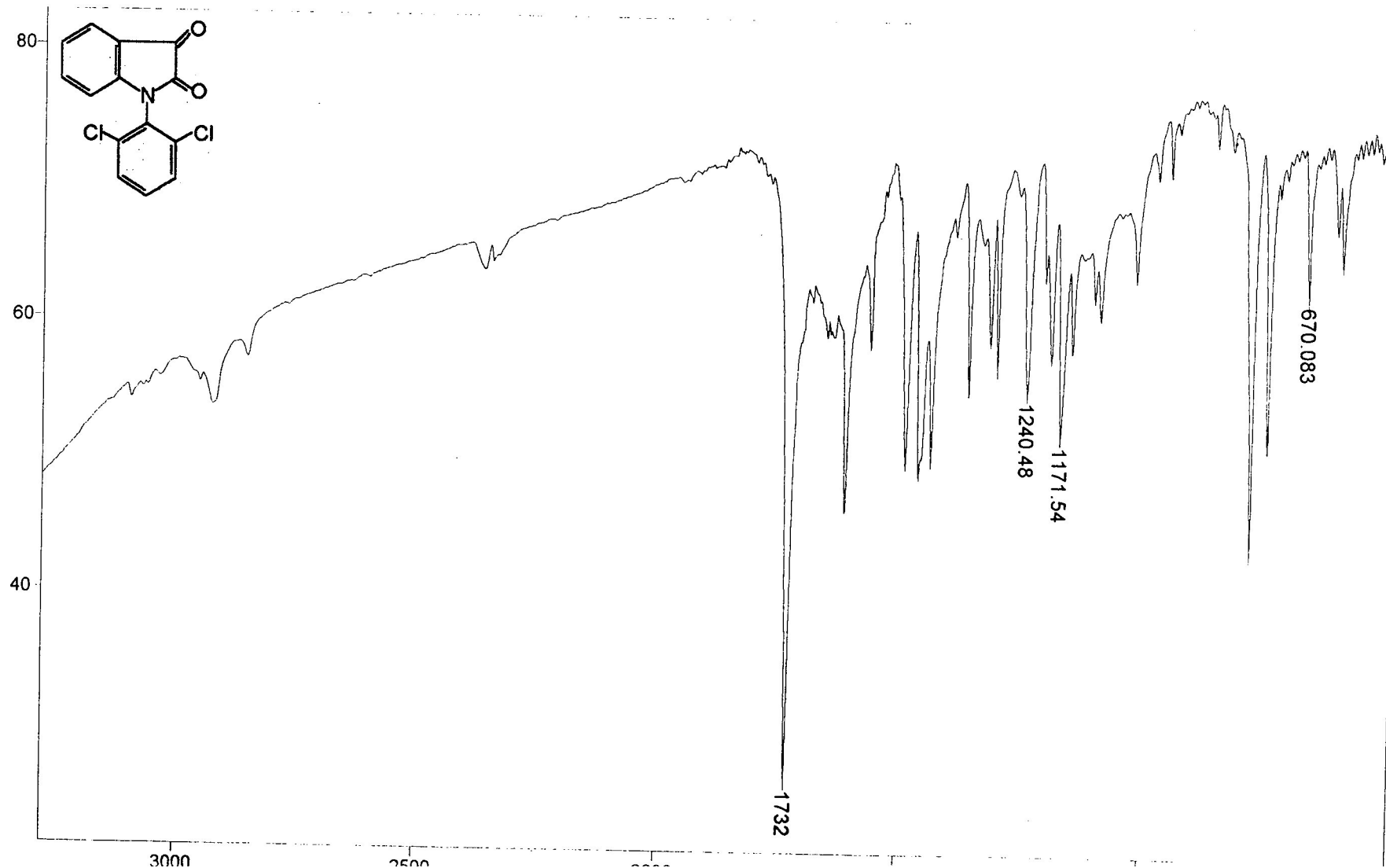
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Scans= 10 Slow

Res=4 cm-1

Apod= Cosine

Zero Filling= 1 x



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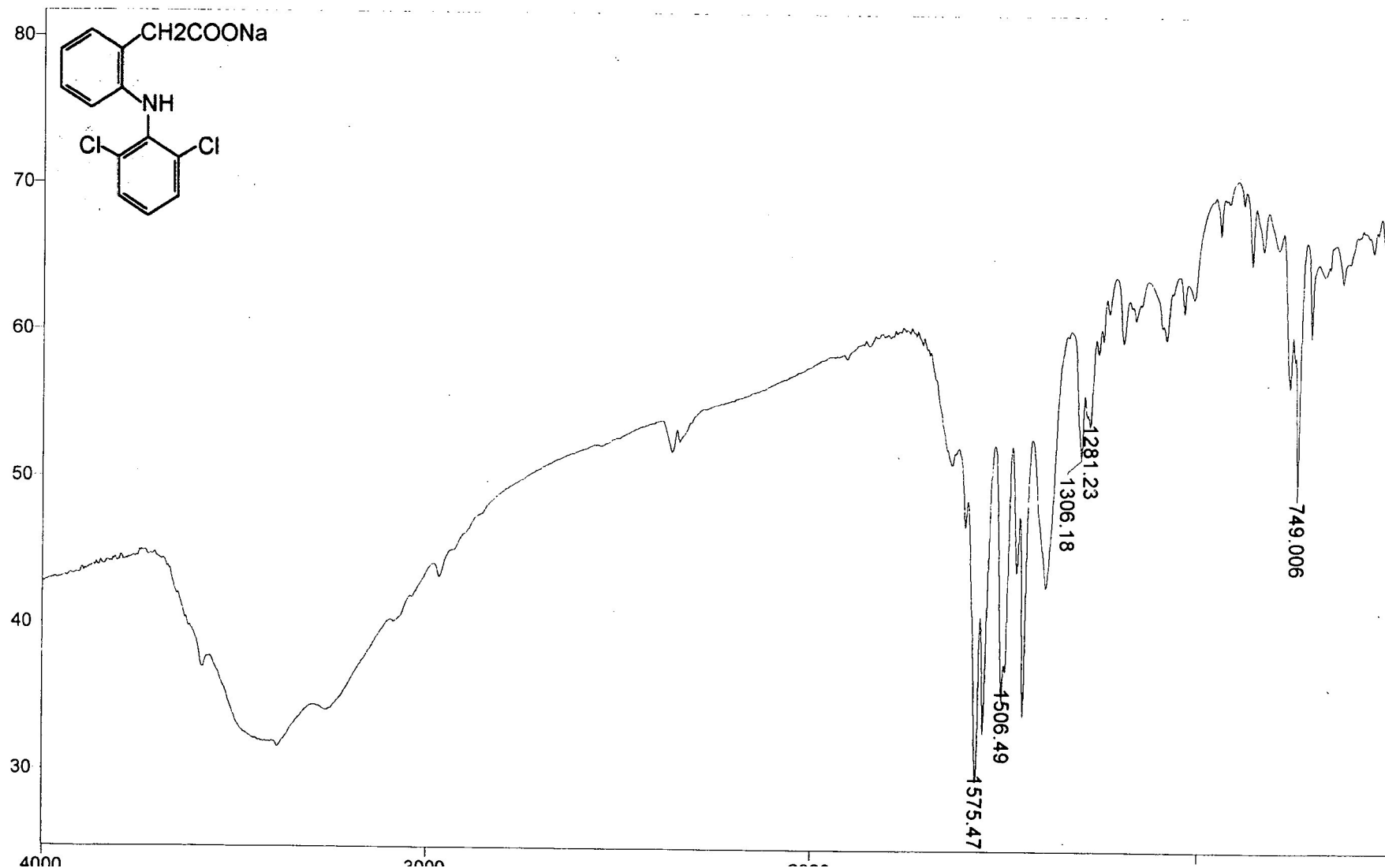
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Scans= 10 Slow

Res=4 cm-1

Apod= Cosine

Zero Filling= 1 x



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Mode= 2 (Mid-IR)

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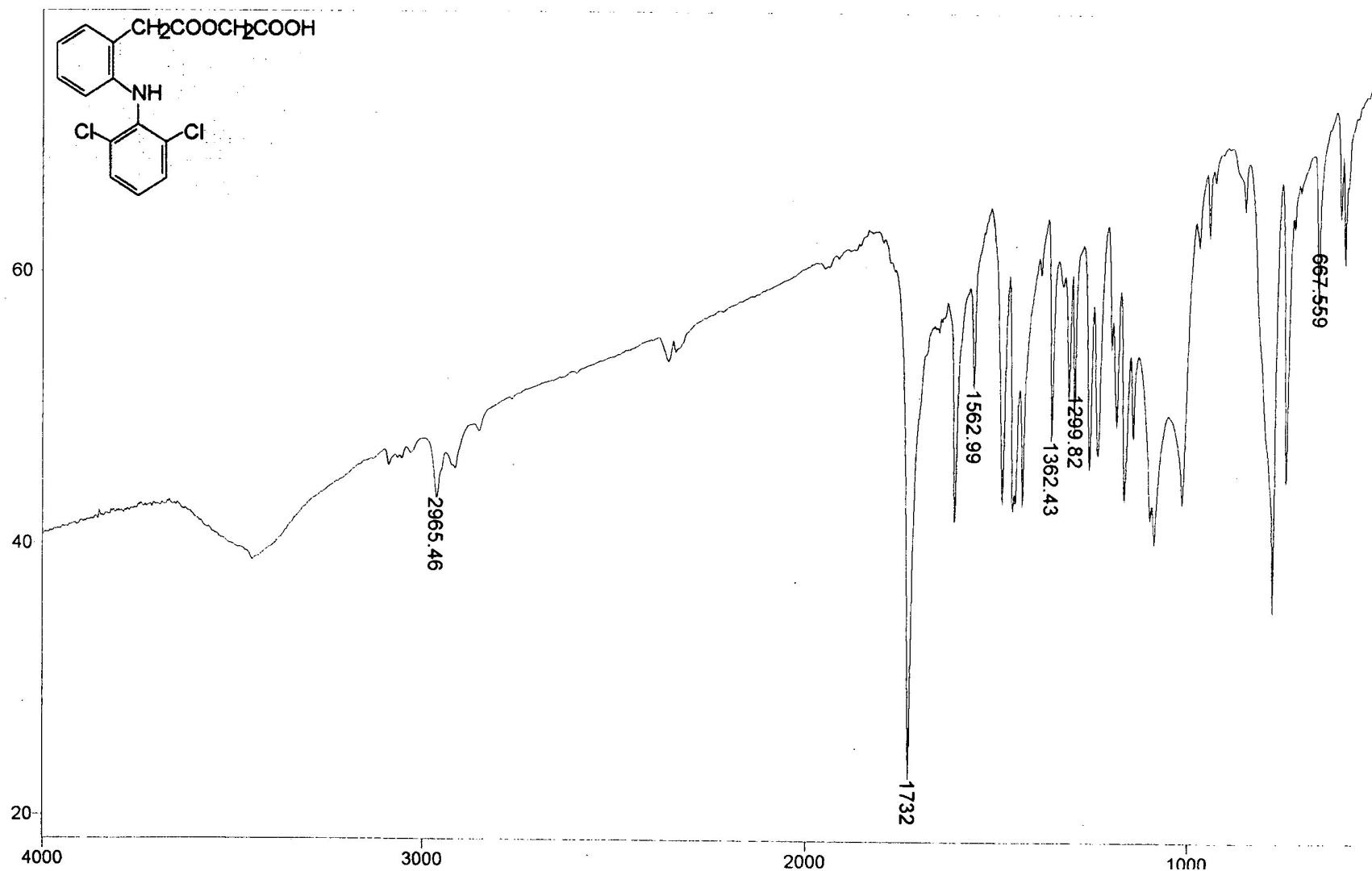
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Scans= 10 Slow

Res=4 cm-1

Apod= Cosine

Zero Filling= 1 x



Results And Discussion

RESULTS AND DISCUSSION

The present study is based on the synthesis of three drug intermediates and an anti-inflammatory analgesic, Aceclofenac.

Though several methods are available for the synthesis of benzophenones but they have their own limitations. The classical methods for the preparation of O-aminoketones, which involved treatment of substituted anilines with acid chlorides, were explored. The following modifications were carried out during workup of the reaction procedures :

1. So as to eliminate excess of acid chloride, as reported in literature method, three hot water washings, each of two hours were given. This was modified and only two fifteen-minute washings with hot water, followed by treatment with 5N sodium hydroxide solution. All this work can be accomplished in one hour, which saves five cumbersome hours.
2. During the work up for 2-amino-2'-fluoro-5-chlorobenzophenone, according to literature reports, reaction mixture is to be dumped in water and then it is extracted with dichloromethane and extracts are washed with 3N hydrochloric acid. It is further washed with 5N sodium hydroxide solution and finally with saturated sodium chloride solution. This work up was found to be hazardous, costly and pollution prone. This was deleted and replaced with cold water treatment of the reaction mass followed by neutralization with sodium bicarbonate and 5N sodium hydroxide solution. Thus, major drawbacks were eliminated in the procedure.
3. During work up for 2-amino-2'-chloro-5-nitrobenzophenone, according to literature procedure, reaction mixture is to be dumped in water, then extracted with organic solvents like benzene or ethyl acetate. The organic layer is treated with sodium bicarbonate solution and the organic solvent is evaporated to obtain the crude product. In our laboratory, we dumped the reaction mixture in ice-cold water. The supernatant was decanted and the solid was suspended in 5% sodium hydroxide solution. However, solvent extraction which is a costly and hazardous method in chemical industry is deleted and replaced with cold water treatment of the reaction mass followed by washings with sodium hydroxide solution. This makes the

process less hazardous, simpler and economical. After five minutes, the solid was collected by filtration.

Visualizing the need for the fine chemical, 2-chloro-1-(4-fluorobenzyl) benzimidazole, it was decided to develop a suitable method for its synthesis. Alkylation of 2-chlorobenzimidazole has been reported using sodium hydride and dimethylformamide. Sodium hydride is a costly, flammable and moisture sensitive solid. Also work up with dimethylformamide is fairly messy and time consuming. This increases the cost of production and handling hazards at industrial scale. In our laboratory, we carried out the reaction in a modified solvent system, i.e. dioxane and dimethylformamide(9:1). This change in the solvent system allowed the reaction to occur at a slightly faster rate. It was also found that the final product which was obtained was relatively free of impurities with a sharp melting point. This effectively helps to cut cost as regards the time and amount of solvent needed for purification of final product.

Method 1 listed in literature survey of Diclofenac sodium was selected for developing a suitable process for scaling up of synthesis of Aceclofenac.

The method utilized for synthesis has a number of advantages :

1. Raw materials such as 2,6-dichloroaniline and bromobenzene are not expensive and are available at fairly economic prices.
2. Minimum number of reaction steps are involved in the preparation.
3. The reactions are simple and do not require any specialized equipment.
4. The reaction conditions are suitable for large scale preparation and are non-hazardous.
5. The yields of the intermediates and the final product are satisfactory.

In literature, for synthesis of Aceclofenac, esterification of Diclofenac was carried out using bromoacetic acid. The crude product obtained was recrystallised from cyclohexane. But in our laboratory, purification of the crude product was carried out by elution of the material in benzene on silica gel column. This avoids the use of the costly solvent, cyclohexane.

Hence, this research project has given successful leads in pursuing the most economic and feasible procedures for the synthesis of 2-amino-substituted benzophenones, 2-chloro-1-(4-fluorobenzyl)benzimidazole and Aceclofenac. We have been able to achieve the final desired products and important intermediates in fairly good yields. This research venture was a sincere exercise towards developing new processes that could be scaled up to industrial levels. At the same time it is observed that these modified procedures are non-hazardous, non-polluting, less time consuming, economic and feasible with the fine chemicals available indigenously.

References

REFERENCES

1. H.L. Bhalla, *IDMA Bulletin XXVI*, **25**, 787-791.
2. Simon De Bree, *Chemical Management and Review*, Schnell Publishing, New York, **1**, 20-23, **1999**.
3. R.J. Baldessarini, Goodman and Gillmans "*The pharmacological Basis Of Therapeutics*", **1**, 8th Edition, MC Graw Hill, New York, 383,428.
4. Wilson Gisvolt's "*Text Book Of Organic Medical And Pharmaceutical Chemistry*", 8th Edition, Lippincott, U.S.A., 365, **1982**.
5. R.L. Jacoby and K.A. Niefofth "*Principles Of Medicinal Chemistry*", W.O. Foye , 3rd Edition, 213.
6. Martindale "*The Extra Pharmacopoeia*", 29th Edition, 708.
7. Erle, *Eur. J. Clin. Pharmac.*, **11**,15, **1977**.
8. L.H. Sternbach, E.I. Fryer, *J. Org. Chem.*, **27**, 3787, **1962**.
9. L.H. Sternbach, E. Reeder, *J. Org. Chem.*, **26**, 111, **1961**.
10. S.A. Kaplan, M. Lewis, *J. Pharm. Sci.*, **59**,1569, **1970**.
11. MacDonald, A.F. Michaelis and B.Z. Senkowski, *Analytical Profiles Of Drug Substances (Florey)*, **1**, 77-99.
12. H.J. Roth and A. Kleeman, *Pharmaceutical Chemistry : Drug Synthesis*, **1**, 313.
13. E.A. Swinyard, *Remington's Pharmaceutical Sciences*, 18th Edition, Mack Publishing Company, Pennsylvania,1058.
14. R.S. Satoskar and Bhandarkar, *Pharmacology and Pharmacotherapeutics*, 11th Edition, 90.
15. R. McDonald and J.C. Barker, *Nature*, 271,563, **1978**.
16. W.C. Bowman, *Textbook Of Pharmacology*, 2nd Edition, Ackwell Scientific Publication, 15.1,15.20.
17. N. Blazeric and D. Kobali, *J. Med. Chem.*, **22**, 1093, **1979**.
18. L.H. Sternbach, *J. Med. Chem.*, **22**, 1, **1979**.
19. J.C. Garrison, "*The Pharmacological Basis Of Therapeutics*", 8th edition, A.G. Gillman, New York, Pergamon Press, 1990.
20. J.R. Cunha-Mello, *J. Biol. Chem.*, **262**, 11455, **1987**.
21. H.H. Dale, P.P. Laidlaw, *J. Physiol.*, **41**, 381, **1910**.

22. H.H. Dale, P.P. Laidlaw, *J. Physiol.*, **43**, 182, **1911**.
23. T.T. Quach, *Eur. J. Pharmacol.*, **60**, 391, **1979**.
24. A.A. Carr, D.R. Meyer, *Drug Research*, **32**, 1157, **1982**.
25. J.C. Garrison, "*The Pharmacological Basis Of Therapeutics*", 8th edition, A.G. Gillman, New York, Pergamon Press, 1991.
26. D.A. Walsh, *J. Med. Chem.*, **32**, 105, **1989**.
27. P.M. Brooks, W.W. Buchanan, N.M. Halder, *Arthritis And Society*, Butterworths, London, 215, **1985**.
28. R.J. Grylgewski, *Agents Action, Suppl.3*, 21, **1977**.
29. K. Brune, M. Glatt and P. Graf, *J. Pharmacol.*, **7**, 28, **1976**.
30. K.D. Rainsford, *Aust. J. Pharm.*, **56**, 375, **1975**.
31. H.E. Paulus and M.W. Whitehouse, *Search For New Drugs*, **6A**, Marcel Dekker, New York, 28, **1972**.
32. R.A. Sherrer, R.A. Scherrer and M.W. Whitehouse, *Min Anti-Inflammatory Agents*, **1**, Academic Press, London, 77, **1974**.
33. N. Koch-Weser, *Engl. J. Med.*, **295**, 1297, **1976**.
34. J.R. Vane, *J. Allergy clin. Immunol.*, **58**, 691, **1976**.
35. G.H. Harmor "*Principles Of Medicinal Chemistry*", W.O. Foye, 2nd Edition, 561, **1981**.
36. *Annual Reports In Medicinal Chemistry*, **27**, James Bristol, Academic Press, 1, **1991**.
37. Burger's "*Medicinal Chemistry And Drug Discovery*", 5th Edition, **2**, Manfred Wolf, Willey-Intersciences, 127.
38. H.R. Howard, T.F. Seeger, *Annual Reports In Medicinal Chemistry*, **28**, Academic Press, London, 39, 325, **1993**.
39. *Annual Reports In Medicinal Chemistry*, **29**, James Bristol, Academic Press, 1994, **1994**.
40. *Drugs Of Future*, **21(8)**, Prous Science, Philadelphia, 799-801, **1996**.
41. *Drugs Of Future*, **23(9)**, Prous Science, Philadelphia, 769-968, **1998**.
42. *Drugs Of Future*, **23(8)**, Prous Science, Philadelphia, 914, **1998**.
43. M. Grau, J. Gausch, J.L. Montero, A. Felipe, *Drug Research*, **41**, 1265, 1275, **1991**.

44. K. Dziewonsky and L. Sternbach, *Über Die Einwirkung Von Benzoyl Chloride Auf Naphthyl Amine*, **1993**. Cited from : C.A., **28**, 2717 (1934), *Ibid*, **30**, 2971 (1936).
45. K. Dziewonsky and L. Sternbach, *Bull. Intern acda. Polonaise, Classe Sci., Math. Nat.*, 1953A, 333, **1934**, Cited from : C.A., **30**, 2972.
46. S.C. Iacobescu, D. Bellu, F. Cuiban, *25th Sci Pharm. Proc.*, **1**, **1965**, Fr., 233, Cited from : C.A., **69**, 27043c.
47. Bogdan Morawiki, *Pol.* **52**, **1966**, 401, Cited from : C.A., **68**, 104757x.
48. L. Kisfaludy, J. Rohricht, A. Andrian, *Hung.*, **1976**, 154, 190, Cited from : C.A., **69**, 27043c.
49. B. Novak, D. Babic, M. Japelji, V. Tisler, E. Kardelja and Do. Krka, *Hem Ind.*, **34 (12)**, **1980**, 330-6, Cited from : C.A., **94**, 191854c.
50. Staskun, *J. Org. Chem.*, **29(10)**, 2856-2860, **1964**.
51. *Organic Synthesis, Col. Vol. IV*, 34-38.
52. B.K. Mishra and V. R. Rao, *Indian Journal Of Chemistry*, **18B**, 19-21, **1979**.
53. E. Giovannini, J. Rosales, B. Desouza, *Helv. Chim. Acta*, **54(7)**, Ger., 2111-2113, **1979**.
54. E. Giovannini, J. Rosales, B. Desouza, *Helv. Chim. Acta*, **62(1)**, Ger., 185-197, **1979**.
55. R. Baruah, J.S. Sandhu, G. Thyagarajan, *J. Hetrocycl. Chem.*, **16(5)**, 1087-1088, **1979**.
56. T. Sugasawa, T. Toyoda, M. Adachi and K. Sasakura, *Ger Offen*, 2, 707, 102, **1977**, Cited from : C.A., **87**, 184218c.
57. J.C.E. Simpson and (in part), C.M. Atiknson, K. Schofield and D. Stephenson, *J. Chem. Soc*, 646., **1945**.
58. Konwar, R.C. Boruah, J.S. Sandhu and J.N. Baruah, *Synthetic Communications*, **14(11)**, 1053-8, **1984**.
59. G.N. Wakker, *J. Org. Chem.*, **27**, 1929, **1962**.
60. D.M. Belu, S.C. Iacobescu, *Rom* 54, **1973**, Cited from : C.A., **80**, 59695k.
61. K. Reisinger, M. Pulster, *Ger Offen*, 2, 400, 689, **1975**, Cited from : C.A., **84**, 43633k.
62. F. Jugestan, I. Niman, E. Koos, *RO.82*, 486, **1983**, Cited from : C.A., **101**, 130397z.

63. A. Novacek, Czech. 164, 184, **1976**, Cited from : C.A., **80**, 106178e.
64. J.B. Wright, *Chem. Rev.*, **48**, 377-541, **1951**.
65. K. Hofmann, *The. Chem. Of Heterocyclic Compounds Part 1*, Weissbeger, Interscience, 247, **1953**.
66. E.S. Schipper and A.R. Day, *Heterocyclic Compounds*, **5**, R.C. Elderfield, N.Y. Willey, 267, 281-84, **1957**.
67. A.F. Pozhanskii, A.D. Garnovskii and A.M. Simmonov, *Russ. Chem. Rev.*, **35**, 122, **1966**.
68. M.R. Grimmett, *Int. Rew. Sci. Org. Chem.*, Med. Tech. Publishing Co., Seroney, **1973**.
69. P.N. Preston, *Chem. Rev.*, **74(3)**, 297-316, **9714**.
70. O. Fischer and O. Veiel, *Ber.*, **38**, **1905**.
71. M.A. Phillips, *J. Chem. Soc.*, **28**, 2820, **1929**.
72. H. Green, A.R. Day, *J. Am. Chem. Soc.*, **64**, 1167, **1947**.
73. R.L. Mc-Kee, R.W. Bost, *J. Am. Chem. Soc.*, **65**, 471, **1947**.
74. W.A. Sexton, *J. Chem. Soc*, 471., **1942**.
75. A.M. Sinsminov, V.A. Ismailskill, C.A., **35**, 2870, **1941**.
76. R.A.B. Lopeland, A.R. Day, *J. Am. Chem. Soc.*, **65**, 1872, **1943**.
77. E.L. Hollegas, E.C. Wagner, *J. Org. Chem.*, **9**, 31-49, **1944**.
78. J.B. Wright, *J. Am. Chem. Soc.*, **71**, 2035, **1949**.
79. R.C. Widerfield, F.J. Kersya, *J. Am. Chem. Soc.*, **70**, 44, **1948**.
80. O. Kymi, *J. Pract. Chem.*, **75(2)**, 323, **1907**.
81. S.M. Ministry, P.C. Ghua, *J. Ind. Chem. Soc.*, **7**, 793, **1930**.
82. Omar, M.E. Hosen, H.S. Habib and A. Omaimam, *Synthesis*, 864-5, **1977**.
83. W.G. Bywater, D.A. MC-Givity and M.D. Jensei, *J. Pharmacol*, **85**, 14, **1945**.
84. Y. Kawakoka, *J. Ind. Chem. Soc.*, **43**, Suppl., **1940**, 275, Cited from : C.A., **35**, 2368, (1941).
85. O. Kym, *J. Pract. Chem.*, **75(2)**, 324, **1907**.
86. O. Billeter, A. steiner, *Ber.*, **20**, 229-231, **1887**.
87. J.G. Everett, *J. Chem. Soc*, 677., **1929**.
88. K. Egon, L. Gunter, C.A., **120**, 164172e, **1994**.
89. A.C. Cope, *Org. Synth.*, **30**, Jhon Wiley And Sons, 56.
90. D.S. Deshpande, *Acta Ciencia Indica*, **5c**, No.2, **80**, **1980**.

91. Harrison, J.T. Ralph and A.C.B. Smith, *J. Chem. Soc.*, **85**, 2930, **1963**.
92. C.A. Parrodi, L.Q. Cortes, R.J. Sandoval, *Synthetic Communications*, **26(17)**, 3326, **1996**.
93. G.Crank, T. Mursydi, *Aust. J. Chem.*, **35**, 775, **1982**.
94. A.A. Jesus, C.A. Issac, S.A. Felix, Span. Pat., 544, 320, **1986**, Cited from : C.A., **106**, 84601q.
95. M.I. Fernandez, M. Izquiereo, A. Martinez, C. Fuentes, M.L. Lucero, Span. Pat. ES 534, 276, 18548b, **1985**, Cited from : C.A., **105**, P.18548b.
96. J. Arin, I. Csent, A. Fernandez, T. Torres, F. Sanchez, Span. Pat., ES 544, 320, **1985**, Cited from : C.A., **106**, P. 84601q.
97. Janssen, J. Torremans, R.A. Stokbroekx, *J. Med. Chem.*, **28**, 1927, **1985**.
98. J.R. Geigy, A.G. Brit, 1, 132, 318, **30 Oct. 1968**, Cited from : C.A., **70**, 57455b.
99. A. Sallmann, R. Pfister (Geigy, J.R.A.-G), S. African, 6705987, **23 Jul. 1968**, Cited from : C.A., **70**, 77619m.
100. J.R. Geigy, A.G. Neth. Appl, 6, 604, 752, **Oct. 10 1966**, Cited from : C.A., **67**, 81925p.
101. A. Sallaman, R. Pfister, (Geigy, J.R.A.-G), Ger. Offen., 1, 815, 802, **10 Jul. 1969**, Cited from : C.A., **72**, 12385d.
102. T. Shimazaki (Daito Koeki Co. Ltd.), Japan Kokai Tokkyo Koho, 7973750, **13 Jun. 1979**, Cited from : C.A., **92**, 6251d.
103. A. Sallmann, R. Pfister (Ciba-Geigy A.-G.), Ger. Offen., 2, 144, 641, **16 Mar. 1972**, Cited from : C.A., **77**, 19403u.
104. T. Okada, K. Naito, T. Kikuchi, Japan Kokai Tokkyo Koho, 7912342, **30 Jan. 1979**, Cited from : C.A., **91**, 5026b.
105. T. Matsumura, Japan Kokai Tokkyo Koho, 7, 961, 143, **17 May 1979**. Cited from : C.A., **92**, 94068c.
106. Nohara, Japan Kokai Tokkyo Koho, 8013227, **30 Jan. 1980**, Cited from : C.A., **93**, 26188q.
107. T. Okada and others, Japan Kokai Tokkyo Koho, 7916441, **7 Feb. 1979**, Cited from : C.A., **91**, 39142b.
108. I. Hashiba and others, Japan Kokai Tokkyo Koho, 78, 84, 936, **26 Jul. 1978**, Cited from : C.A., **90**, 6104s.

109. I. Hashiba and others, Japan Kokai Tokkyo Koho, 79, 73, 737, **13 Jun 1979**, Cited from : C.A., **91**, 192969w.
110. I. Hashiba and others, Japan Kokai Tokkyo Koho, 79, 73, 711, **13 Jun 1979**, Cited from : C.A., **91**, 193174v.
111. Hashiba and others, Japan Kokai Tokkyo Koho, 7963041, **21 May 1979**, Cited from : C.A., **91**, 193174v.
112. K. Tamura, Japan Kokai Tokkyo Koho, JP, 82, 75, 954, **12 May 1982**, Cited from : C.A., **97**, 162590x.
113. Y. Fujimoto and others, Japan Kokai, 7771439, **14 Jun 1977**, Cited from : C.A., **87**, 167745e.
114. Organisation Fuer Chemic and Galenic A.-G. Patents-Chrift (Switz) CH 646,413, **30 Nov. 1984**, Cited from : C.A., **102**, 113051k.
115. Y. Kato, T. Shinuchi, Japan Kokai, 7768142, **6 Jun. 1977**, Cited from : C.A., **87**, 151859i.
116. Toro Yakhun K.K., Japan Kokai Tokkyo Koho JP, 81158744, **7 Dec. 1981**, Cited from : C.A., **97**, 234672.
117. Mori and others, Japan Kokai, 7807640, **24 Jan. 1978**, Cited from : C.A., **88**, 190410w.
118. M. Takeda and others, Japan Kokai Tokkyo Koho, 7955543, **2 May 1979**, Cited from : C.A., **91**, 192998e.
119. Y. Hasegawa and others, Japan Kokai Tokkyo Koho, 7868741, **19 Jun. 1978**, Cited from : C.A., **89**, 146622p.
120. Daito Koeki Co. Ltd., Japan Kokai Tokkyo Koho, 80987748, **2 Jul. 1980**, Cited from : C.A., **94**, 303739.
121. K. Ohira and others, Japan Kokai Tokkyo Koho, 7973749, **13 Jun. 1979**, Cited from : C.A., **92**, 6252e.
122. Taiyo Yakuhin Kogyo K.K., Japan Kokai Tokkyo Koho, 8072152, **30 May 1980**, Cited from : C.A., **94**, 83783x.
123. Yamagami and others, Japan Kokai, 7700240, **5 Jan. 1977**, Cited from : C.A., **87**, 39078c.
124. Hamari Yakuhin Kogyo K.K., Japan Kokai Tokkyo Koho, 80, 66, 551, **20 May 1980**, Cited from : C.A., **93**, 167947w.
125. A. Sallmann and R.P. Fister (Giegy, J.R. A.-G.), S. African, 6705989, **26 Apr. 1968**, Cited from : C.A., **71**, 12836f.

126. T. Oe and others, Japan Kokai, 77153929, **21Dec. 1977**, Cited from : C.A., **88**, 136321e.
127. K. Arimura and T. Kawakita, Japan Kokai, 77153928, **21Dec. 1977**, Cited from : C.A., **88**, 136322f.
128. K. Arimura and others, Can., 1095077, **3 Feb. 1981**, Cited from : C.A., **95**, 97376z.
129. G. Kimizuka and Y. Kumae, Japan Kokai Tokkyo Koho, 79, 125, 634, **29 Sept. 1979**, Cited from : C.A., **92**, 110688n.
130. Permachem Asia Ltd, Japan Kokai Tokkyo Koho, 80, 108, 845, **21 Aug. 1980**, Cited from : C.A., **94**, 174668e.
131. P.L. Pedro and G.B. Elisa, Span, 480874, **1 Feb. 1980**, Cited from : C.A., **93**, 204276z.
132. Nissan Chemical Industries, Japan Kokai Tokkyo Koho, 8087765, **2 Jul 1980**, Cited from : C.A., **94**, 102993j.
133. Zenyaku Kogyo Co. Ltd., Japan Kokai Tokkyo Koho, JP 82, 152, 445, **26 Nov. 1981**, Cited from : C.A., **96**, 122429z.
134. Zenyaku Kogyo Co. Ltd., Japan Kokai Tokkyo Koho, JP 82, 64, 647, **19 Apr. 1982**, Cited from : C.A., **97**, 91911q.
135. T. Matsumura and others, Japan Kokai, 7759131, **16 May 1977**, Cited from : C.A., **87**, 151858h.
136. T. Matsumura and others, Japan Kokai Tokkyo Koho, 79, 123, 40, **30 Jan. 1979**, Cited from : C.A., **91**, 20124a.
137. Y. Fujimori and others, Japan Kokai Tokoyo Koho, 8022629, **18 Feb. 1980**, Cited from : C.A., **93**, 71302f.
138. Daito Koeik Co. Ltd, Japan Kokai Tokoyo Koho, 8085547, **27 Jun. 1980**, Cited from : C.A., **93**, 167950s.
139. T. Matsumura and others, Japan Kokai Tokkyo Koho, 7912341, **30 Jan. 1979**, Cited from : C.A., **91**, 39141a.
140. T. Matsumura and others, Japan Kokai Tokkyo Koho, 7961, 144, **17 May. 1979**, Cited from : C.A., **91**, 193004q.
141. K. Suzuki, Japan Kokai Tokkyo Koho, 79157538, **12 Dec. 1979**, Cited from : C.A., **93**, 71299k.
142. S. Miyahara and Y. Yamada, Japan Kokai Tokkyo Koho, 79, 109, 942, **29 Aug. 1979**, Cited from : C.A., **92**, 163716b.

143. Y. Ono and others, Japan Kokai Tokkyo Koho, 7930131, **6 Mar. 1979**,
Cited from : C.A., **91**, 56641f.
144. Mitsui Toatsu Chemicals Inc., Japan Kokai Tokkyo Koho, 80, 136,
255, **23 Oct. 1980**, Cited from : C.A., **94**, 208553f.
145. K.Yagami and others, Japan Kokai Tokkyo Koho, 8020727,
14 Feb. 1980, Cited from : C.A., 93, 71309p.
146. Y. Ono and others, Japan Kokai Tokkyo Koho, 7930137, **6 Mar. 1979**,
Cited from : C.A., **91**, 56640e.
147. F. Nohara, Ger. Offen., 2, 613, 838, **7 Oct. 1976**, Cited from :
C.A., **86**, 43412d.
148. Y. Kato and others, Japan Kokai, 76141, 835, **7 Dec. 1976**,
Cited from : C.A., **86**, 189526r.
149. Y. Fujimori and Y. Otsuga, Japan Kokai, 7783425, **12 Jul. 1977**,
Cited from : C.A., **87**, 201110f.
150. K. Sakakibara and others, Japan Kokai, 7807641, **24 Jan. 1978**,
Cited from : C.A., **86**, 190399z.
151. Japan Kokai Tokkyo Koho, 7909238, **24 Jan. 1979**, Cited from :
C.A., **91**, 201232.
152. Y. Ono, F. Nishimura, Japan Kokai Tokkyo Koho, 79, 66, 651,
29 May. 1979, Cited from : C.A., **91**, 211094a.
153. Alcar s.r.l., Fr. Demande, 2, 449, 674, **19 Sept. 1980**, Cited from :
C.A., **95**, 115066e.
154. Permachem Asia Ltd., Japan Kokai Tokkyo Koho, 80, 108, 844,
21 Aug. 1980, Cited from : C.A., **94**, 174669f.
155. G.G.Moore, T.A. Folgia and T.J. McGohan, *J. Org. Chem.*, **44**, 2425,
1978.
156. R.C. Larcock, *J. Org. Chem.*, **41**, 1373, **1976**.
157. R.C. Larcock, *J. Org. Chem.*, **39**, 3721, **1974**.
158. R.C. Merker and M.J. Scoh, *J. Org. Chem.*, **26**, 5180, **1961**.
159. E. Haslam, *Tetrahedron*, **36**, 2409, **1980**.
160. Baldevkumar, Harshkumar, Anupama Parmar,
Synthetic Communication, **22(7)**, 1087, **1992**.
161. M.A. Ginebreda, C.A. Agusti, Span. Pat. 2, 020, 146, **16 JUL 1991**,
Cited from : C.A., **116**, 173778b.

Appendix

APPENDIX

1. The melting points have been determined in open capillaries in a veego VMP – 1 melting point apparatus and are uncorrected.
2. The Thin Layer Chromatography of the compounds have been run on E. Merck pre-coated silica gel plates of type 60 F 254.
3. Elemental analysis was carried out on Heraeus CHN elemental analyzer (Heraeus, Hanau, Germany) rapid instrument.
4. The Infrared spectra were recorded on a BOMEM MB – 104 Fourier Transform Infrared Spectrometer.
5. The PMR Spectra were recorded Varian 300 MHz. Spectrometer using TMS as internal reference

Synopsis

SYNOPSIS

Today, research in pharmaceuticals is becoming ever more expensive with the result that end products are priced out of reach of people in the developing countries. Yet, pressures from manufacturers and donors to adopt these costly new technologies, and even from general public are intense. In order to economize and develop new approaches, it is essential to do research on the development of new processes modifying the existing ones. It is a medicinal chemist's challenge to carry out modification in such a way that it helps in the development of routes which are not only cost-effective, but also save the time required for the entire process. Besides being cost-effective, the new route must utilize raw materials that are safe and easy to handle on a large scale and which are indigenously available. An equally important aspect of designing new routes is to make use of non-toxic materials and to ensure that the entire process is non-hazardous. The method can also be designed in such a way that along with overcoming these obstacles, it should increase the yield of reaction. Increasing the yield of reaction is by itself a great challenge. Sometimes the entire process may essentially remain the same but its final step may be slightly changed to dramatically improve the yield. Drug intermediates and drugs that can be synthesized by such altered routes will definitely overcome all the obstacles and can be made available at prices that are within the reach of the common man.

The last decade has witnessed an intense activity in the manufacture of several bulk drugs in the country. However, the intermediates required for the manufacture of these drugs, are mostly being imported. The information available on various steps involved in the synthesis of most of these intermediates is very limited and is generally confined to the patent literature. Further, the procedures reported in literature are of preparative nature and may not necessarily be suitable for large scale manufacture. Work was, therefore undertaken on a few important intermediates. These are incorporated into following four parts:

PART I :Synthesis of 2-amino-2'-fluoro-5-chlorobenzophenone.

PART II :Synthesis of 2-amino-2'-chloro-5-nitrobenzophenone.

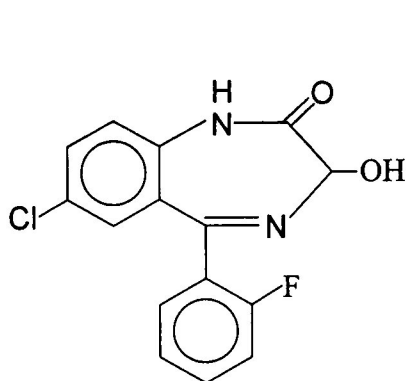
PART III :Synthesis of 2-chloro-1-(4-fluoro benzyl)-benzimidazole.

PART IV :Synthesis of drug intermediates of Aceclofenac and Aceclofenac itself.

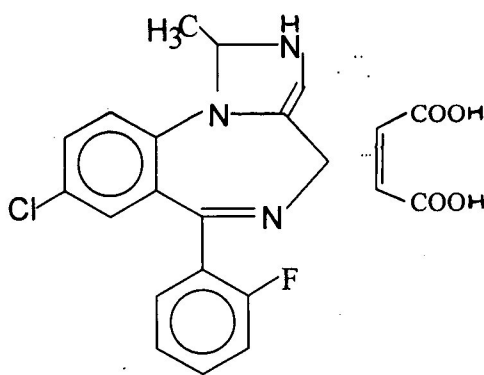
PART I :

Synthesis of 2-amino-2'-fluoro-5-chlorobenzophenone:

Anxiety is treated by benzodiazepines¹.The discovery of novel atypical antipsychotic agents with efficacy against both positive and negative symptoms, along with reduced side effects profile, remains a primary goal in the treatment of schizophrenia².A number of reviews have appeared which cover emerging therapies as well as clinical performances of more advanced candidates like Cinolazepam(I) and Midazolam maleate(II)³⁻⁴.



(I)



(II)

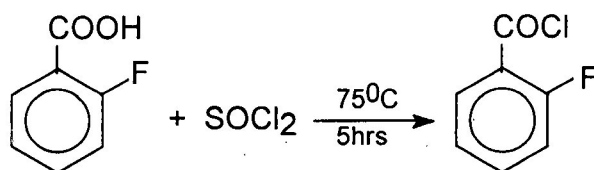
Synthesis of such useful drugs start from 2-amino-2'-fluoro-5-chlorobenzophenone. However, at present it is totally imported and there is a great need to develop a simplified preparative process for this specialized fine chemical from readily available raw materials. In literature, no much details are reported. Hence, synthesis of this compound was carried out in our laboratory by a different method to get improved yield.

This intermediate is also useful for synthesis of following drugs:

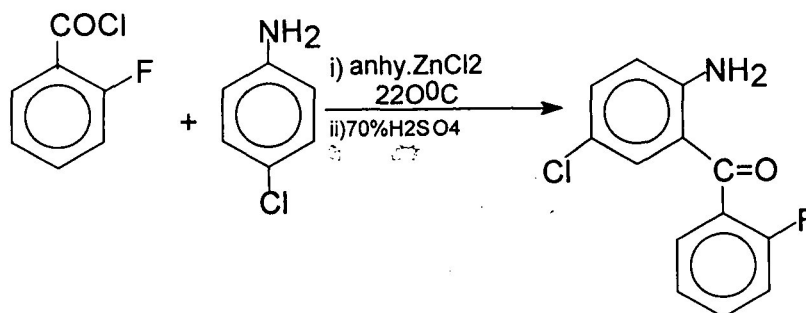
Eflazepam, Kenazepin, Flurazepam, Flutoprazepam, Fludiazepam, Midolazepam, Quazepam, Oxoqueazepam and Doxefazepam.

The synthesis involves two steps :

1) Preparation of 2-fluoro benzoyl chloride :



2) Preparation of 2-amino-2'-fluoro-5 chlorobenzophenone:



The following modifications were made in our laboratory:

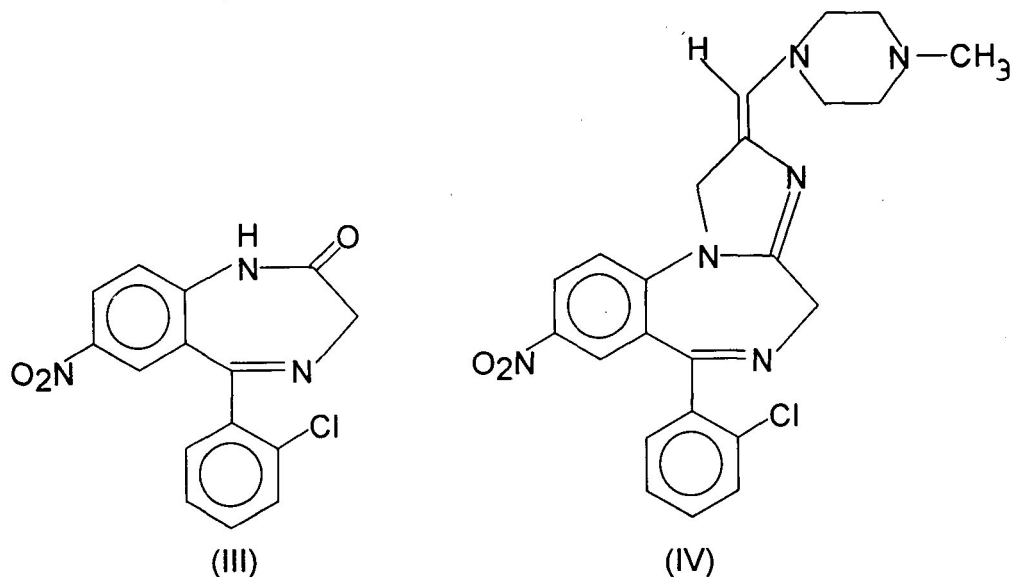
1) So as to eliminate excess of acid chloride, as reported in literature method, three hot water washings, each of two hours are given. This was modified and only two fifteen-minutes washings of hot water, followed by treatment with 5N sodium hydroxide solution was given. All this work can be accomplished in one hour, which saves five cumbersome hours.

2) During the work up, according to literature reports, reaction mixture is to be dumped in water, then it is extracted with dichloromethane and extracts are washed with 3N hydrochloric acid, then with 5N sodium hydroxide solution and finally with saturated sodium chloride solution. This work up was found to be hazardous, costly and pollution prone. This was deleted and replaced with cold water treatment of the reaction mass followed by neutralization with sodium bicarbonate and 5N sodium hydroxide solution. Thus, major drawbacks of the procedure were eliminated.

PART II :

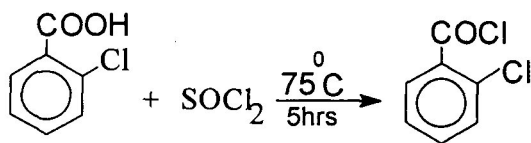
Synthesis of 2-amino-2'-chloro-5-nitrobenzophenone:

This fine chemical serves as drug intermediate for vital benzodiazepines like Clonazepam(III) and Loprazolam(IV).

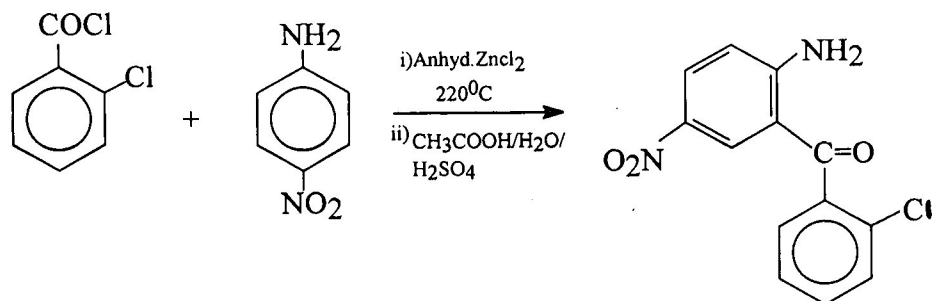


Since 2-amino-2'-chloro-5-nitrobenzophenone is not being manufactured in India, there exists scope for its development. Hence, laboratory method of synthesis of 2-amino-2'-chloro-5-nitrobenzophenone was undertaken. Synthesis involves two steps :

1) Synthesis of 2-chloro benzoylchloride:



2) Preparation of 2-amino-2'-chloro-5-nitrobenzophenone:



Modifications:

1) In literature method, three hot water washings, each of two hours, have been given. In our laboratory we gave two fifteen minutes washings of hot water followed by treatment with 5% sodium hydroxide solution. This eliminates unreacted 2-chlorobenzoylchloride. All this work can be accomplished in one hour, which saves five cumbersome hours.

2) During work up, according to literature procedure, reaction mixture is to be dumped in water, then extracted with organic solvent like benzene or ethyl acetate. The organic layer is treated with sodium bicarbonate solution and the organic solvent is evaporated to obtain the crude product. In our laboratory, we dumped the reaction mixture in ice-cold water. Water was decanted and solid was suspended in 5% sodium hydroxide solution. However, solvent extraction which is a costly and hazardous method in chemical industry is deleted and replaced with cold water treatment of the reaction mass followed by washings with sodium hydroxide solution. This makes the process less hazardous, simpler and economical. After five minutes, the solid was collected by filtration.

PART III :

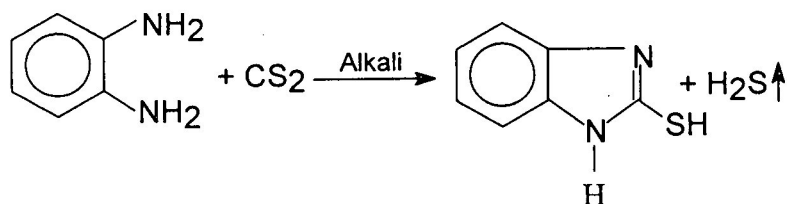
Synthesis of 2-chloro-1-(4-fluorobenzyl)-benzimidazole

Histamine H-1 antagonists were first utilized in the mid to late 1940s and were rapidly established for the treatment of various allergic disorders⁵. Due to sedative effects of classic histamine H-1 antagonists, the pharmaceutical industry embarked upon search for sedation-free H-1 receptor compounds. As a result, over eleven non-sedating antihistamines have been introduced over the last twelve years. Scientists at 'Synthelabo' (F.R.) synthesized a series of benzimidazoles with the aim of obtaining a potent and selective non-sedative histamine H-1 receptor antagonist, and one such compound SL-85.0324(Mizolastine) has been proved to be effective and is being circulated in the U.K. market under the registered name as Mizollen. Another compound of the similar category, named as Norastemizole, has been manufactured by Sepracor, Inc (U.S.) and is currently under clinical studies⁶.

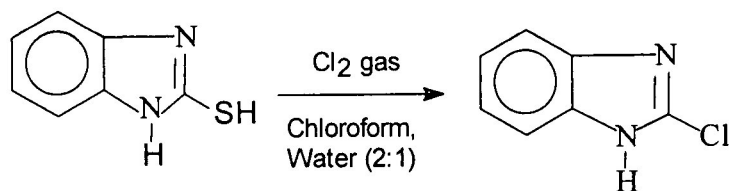
For synthesis of both these drugs, 2-chloro-1-(4-fluorobenzyl)-benzimidazole is used as starting material. Synthesis of intermediate involves following steps:

- 1) Preparation of 2-mercapto benzimidazole.
- 2) Preparation of 2-chloro benzimidazole.
- 3) Addition of 4-fluorobenzyl chloride to 2-chloro benzimidazole.

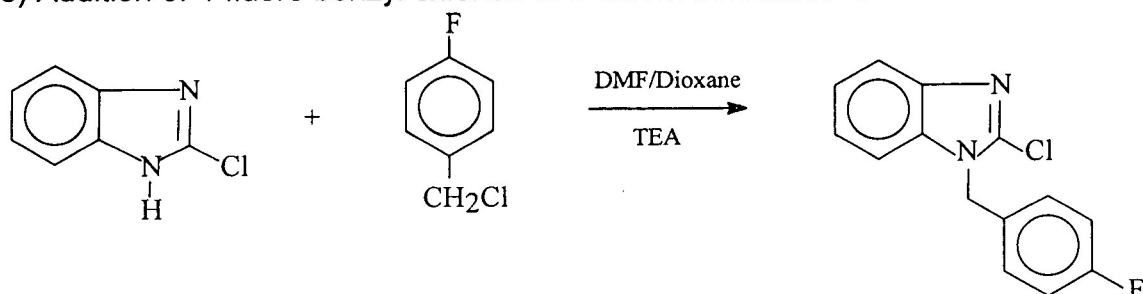
1) Preparation of 2-mercapto benzimidazole:



2) Preparation of 2-chloro benzimidazole:



3) Addition of 4-fluoro benzyl chloride to 2-chloro benzimidazole



Modifications:

In literature, it is reported that the reaction is carried out in sodium hydride and dimethylformamide. Sodium hydride is a costly, flammable and moisture sensitive solid, also work up with dimethylformamide is fairly messy and requires time. This increases the cost of production and handling hazards at industrial scale. In our laboratory we carried out the reaction in a mixed solvent dioxane and dimethylformamide(9:1). This change in the solvent system allowed the

reaction to occur at a slightly faster rate. It was also found that the final product which was obtained was relatively free of impurities and a sharp melting point was obtained. This effectively helps to cut cost as regards the time and amount of solvent needed for purification.

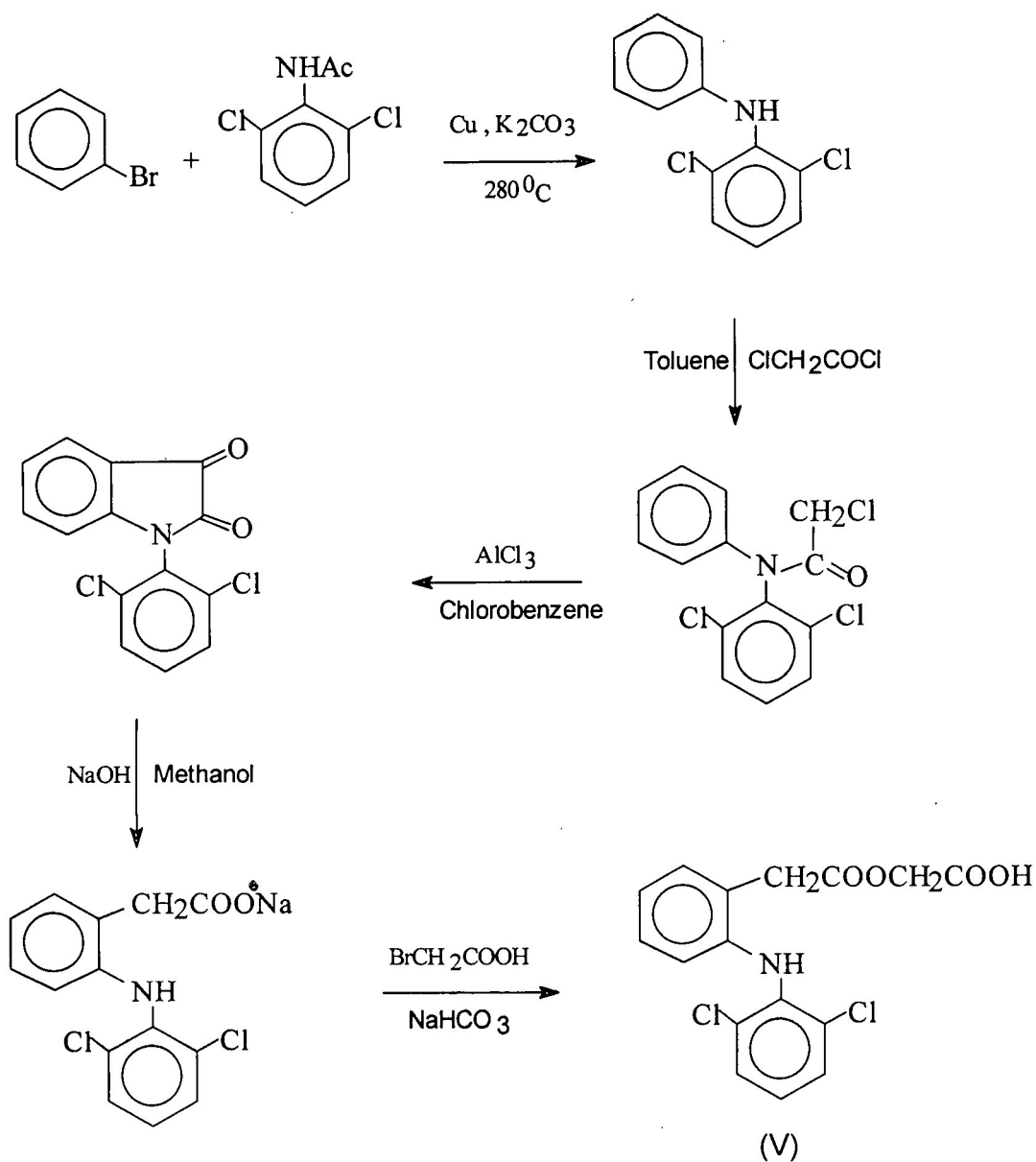
PART IV :

Synthesis of Aceclofenac:

Non-steroidal anti-inflammatory agents are used mainly to control the symptoms of arthritis and related connective tissue diseases⁷. Immunoregulatory agents are increasingly being investigated for their effects on immunologically mediated forms of arthritis, such as rheumatoid arthritis. New compounds in both these classes continue to be discovered in animal models for inflammation. In addition, recent clinical reports have established a number of compounds from both classes as being effective in treating inflammatory diseases⁸.

Aceclofenac is a non-steroidal anti-inflammatory agent with analgesic and antipyretic properties. It is reported to be useful in the treatment of osteoarthritis, rheumatoid arthritis and pain associated with minor surgical procedures. As compared to ketoprofen, Aceclofenac is faster acting in treatment of rheumatoid arthritis⁹⁻¹⁰.

This being an important drug, the synthesis of this compound was indigenously carried out in our laboratory. It can be synthesised by various possible routes¹¹⁻¹², but from our experimental evidences we recommend that the best method for preparation of Aceclofenac(V) is as follows:



Other routes employ the use of chemicals like sodium cyanide and lithium aluminium hydride. Sodium cyanide, a violent poison, is highly toxic and irritant; Similarly, lithium aluminium hydride is flammable liquid and its use requires maintenance of anhydrous conditions which are difficult to maintain on an

industrial scale. Also, since these compounds are required in a relatively large quantity, the process poses environmental hazard, difficulty in handling and lack of safety to the workers and increase in production cost. Hence, this process is not feasible.

REFERENCES

- 1) Sternbach, L. H., *Prog. Drug Res.*, **21**, **1978**, 229.
- 2) Harry R. Howard, Thomas F. Seeger, *Annual Reports in Medicinal Chemistry*, **28**, Academic Press, London, **1993**, 39.
- 3) James A. Bristol, *Annual Reports in Medicinal Chemistry*, **29**, Academic Press, London, **1994**, 1994.
- 4) *Drugs of future*, 23(11), Prous Science, Philadelphia, **1998**, 1252.
- 5) Ming Qiang Zhang, Rob leurs, Henk Timmerman, *Burgers "Medicinal Chemistry and Drug Discovery"*, edited by Manfred E. wolf, 5th edition, Wiley Interscience, New York, 545-546.
- 6) *Drugs of future*, 21(8), Prous Science, Philadelphia, **1996**, 779-804.
- 7) Paul A. Insel, Goodman and Gilmans "*The Pharmacological Basis of Therapeutics*" 9th edition, MC Graw Hill, New York, 617.
- 8) Joshep G. Lambardino, *Annual Reports in Medicinal Chemistry*, **16**, Academic Press, London, **1981**, 189.
- 9) James E F Reynolds, *Martindales "The Extra Pharmacopeia"*, 31st edition, Edited by Kathleen Parfitt, J M Braithwaite and son Limited, West Midlands, **1996**, 13.
- 10) James A. Brisol, *Annual Reports in Medicinal Chemistry*, **28**, Academic Press, London, **1993**, 189.

- 11) Von A. Kleemann, J. Engel, *Pharmazeutische Wirkstoffe*, George Thieme, Verlag Stuttgart, New York, **1982**, 293.
- 12) Flores Ramos, Ramon, Span Pat., 2 046 141 (1994), *Chem. Abstr.*, **121**, **1994**, 35025f.

