ADVANCED PRACTICAL MEDICINAL CHEMISTRY

Ashutosh Kar

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Theory-Methodology-Purification-Usages

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"The Road to Success leads through the Valley of Humility, and the Path is up the Ladder of Patience and Across the Wide Barren Plains of Perseverance. As yet, no Short Cut has been Discovered".

Josheph J Lamb

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PREFACE

The '*art and skill*' for the preparation of '**newer drug molecules**' is a pivotal creative and an exceptionally great intellectual exercise that essentially serves as a fulcrum to plethora of specific areas of scientific research, ranging from the **most applied** to the **most academic**. Accordingly, the medicinal chemist, organic chemist, biologist, pharmacologist, biochemist, biotechnologist, phytochemist, genetic engineer, materials scientist, and polymer scientist, in an university or an industry, all must have genuinely encountered with the most challenging and intricate task of performing a reaction ultimately leading to an entirely new organic preparation exhibiting certain specific actions on the biological system to combat diseases in the ailing human beings.

Invariably, the wonderful 'magic' of modern organic synthesis, based on host of documented theories, hypothesis, organic name reactions (ONRs) amalgamated with logistic, scientific and assertive reaction mechanism(s), in fact, genuinely paved the way of complicated, not-so-easy, cumbersome course of reactions much simpler and understandable.

The advent of ever-more sophisticated and many supportive modern analytical techniques, such as : UV, IR, NMR, MS, ORD, CD, AAS, FES, GC, HPLC and the hyphenated techniques as well, have tremendously enhanced the confidence of medicinal chemists to such a magnitude as to maximize both the chances of success rate and probability factor.

Besides, the use of organic and inorganic chemicals employed as reactants, catalysts, medium of reaction, purifying substances etc., are not only harmful but also hazardous in nature. Nevertheless, the various conditionalities of critical and specific reactions are sometimes articulated and spelled out so meticulously that one has to follow them just like '**gospel truth**', to accomplish the right synthesis, and hence, the right product.

It is, however, pertinent to mention here that the UG and PG students, associated with the myth and reality of '**drug synthesis**' should make an honest attempt to carry out a particular synthesis of a drug substance with a most tried and tested methodical, scientific and rational approach, so that one may get reproducible results under a particular reaction in a seamless manner.

The copious volumes of textbooks, scientific research journals, monographs, review articles on related topics like : organic chemistry of drug synthesis, chiral chemistry, drug design, principles of medicinal chemistry, organic medicinal and pharmaceutical chemistry, and medicinal chemistry provide ample evidence and scope to suggest that the comprehensive in-depth knowledge together with utmost specialized state-of-the-art know-how of the various techniques is an absolute necessity and basic requirement to have a real understanding with regard to the practical aspects of '**Medicinal Chemistry**'.

In '**Advanced Practical Medicinal Chemistry**', an attempt has been made to stress the much needed requirement of both undergraduate and graduate students specializing in the field of Pharmaceutical Chemistry to learn how to synthesize '*drugs*' in the laboratory. Unfortunately, the common available textbooks ordinarily referred to by the **Pharmacy Students**

mostly deal with the synthesis of pure '**organic compounds**' ; and hence, do not provide the real and much needed subject matter relevant to a budding '**Medicinal Chemist**'.

The **'Advanced Practical Medicinal Chemistry'** comprises of *four major chapters* that are intimately associated with specific emphasis on the synthesis of a broad range of some typical and selected '**drugs**' commonly found in the therapeutic armamentarium.

Chapter-1 deals with '*Safety in a Chemical Laboratory*'. It consists of various aspects, namely : guard against personal safety ; conduct in a chemistry laboratory ; neatness and cleanliness ; after-hours working ; guidelines for accident or injury ; storage of chemicals/reagents in a chemical laboratory ; glass ware ; waste disposal ; an ideal chemistry laboratory ; and toxicity and hazards of chemicals/reagents.

Chapter-2 consists of '*Drug Synthesis*'. First, aspect being—'Conceptualization of a Synthesis' *viz.,* prime considerations in designing synthesis ; the Synthon Approach ; reaction specificity. Secondly, Reaction Variants, *viz.,* structural variants ; interchangeability of functional moiety ; selectivity in reactions ; protection of functional moieties ; elimination of functional moieties ; annealation reactions ; fragmentation reactions. Thirdly, Stereochemistry, *viz*., nucleophilic substitutions (SN^2), ionic additions to C-C double bonds ; catalytic hydrogenation ; acid or base promoted enolization of compounds, reductions of cyclohexane ; and cycloadditions.

Chapter-3 comprises of '*Performing the Reactions*'. The wide range of latest laboratory techniques invariably employed in a reasonably well equipped chemical research laboratory or a chemical laboratory for actually performing the specifically desired reactions and other equally important operational measures have been dealt with in an explicit and lucid manner. The various aspects included in this chapter are, namely : solvent stills (with continuous still collecting head)-reactions performed at elevated temperatures-large scale reaction and slow addition of reagents-low temperature reactions-reaction above room temperature using a condenser-mechanical stirrer-mechanical shaker-crystallization at low temperature-distillation under reduced pressure-small scale distillation-performing the reaction, and -photolysis.

Chapter-4 i.e., the last chapter, has been exclusively devoted to—'*Synthesis of Medicinal Compounds*' which vary in length from the single-stage reaction to the multi-stage or project-type synthesis. In fact, it is the backbone of the present textbook and specially designed to inculcate the sense of creativity, learning the art of synthesis, and above all inject the spirit of zeal and enthusiasm amongst the '**medicinal chemists**' to tackle most synthesis-related problems with great ease, confidence and fervour. It embraces '**three**' specific areas of interest confined to the 'synthesis of drugs', such as :

(*a*) *Types of Chemical Reactions* e.g., acetylation methods-benzoylation methods-sulphonation methods-bromination methods-condensation reactions ; and diazotization and coupling reactions ;

(*b*) *Organic Name Reactions* (ONRs) e.g., Bart reaction-Diel's-Alder reaction-Friedel-Craft's reaction-Fries reaction-Grignard reaction-Hoesch reaction-Perkin reaction-Mannich reaction-Michael reaction, and Reimer-Tieman reaction ;

(*c*) *Selected Medicinal Compounds* : It includes the synthesis of **forty** selected medicinal compounds having a wide variety of therapeutic action(s).

An intensive and extensive care has been exercised painstakingly and meticulously to discuss in details each and every medicinal compound under the above mentioned three categories i.e., (*a*) through (*c*) in a particular original style of presentation that essentially includes :

chemical structure-synonym(s)/chemical name(s)-theory-chemicals required-procedure-precautions-recrystallization-theoretical yield/practical yield-physical parameters-uses, and -questions for *viva-voce*.

A subtle, but no less profound effect of this completely new approach as given in the **'Advanced Practical Medicinal Chemistry**' comprising of syntheses totalling **eighty** selected '*drug substances*' would not only benefit the undergraduate and graduate students in Pharmaceutical Chemistry in Indian Universities and other developing countries as well, but also go a along way to help the esteemed teachers involved in the handling of such courses who always genuinely felt the dire necessity of such a compilation for the 'academics' in particular. The '**medicinal chemists**' involved in **'Bulk Drug Manufacturing Operations'** may also find this presentation as a handy reference book in the domain of their ever expanding and demanding profession.

In case, the above outlined objectives have been duly achieved, actual users of this textbook must be able to accomplish their synthetic problems with greater ease and confidence. Synthesis of **'Medicinal Compounds'** is not only satisfying but also exciting, and provides an ample opportunity to explore an individual's inherent talent and enormous strength of '*real creativities'*.

Ashutosh Kar

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CONTENTS

CHAPTER 1

Safety in a Chemistry Laboratory

1.1 INTRODUCTION

A well-designed, well-equipped and strategically located **chemical laboratory** is really a wonderful place for a *research chemist* where one may transform one's conceptualized theoretical novel ideas into sharply evident reality in the shape of useful **'target-drug-molecule'**. The on-going quest for newer **drugs** is an eternal endeavour across the globe to improve the quality of life of human beings irrespective of their caste and creed.

Nevertheless, a chemistry laboratory should not be regarded as a *'dangerous place'* to carry out planned experimental procedures, in spite of the several potential hazards that may be directly or indirectly associated with them, provided that one strictly observes and maintains certain basic fundamental important precautions amalgamated with unusual alertness, extraordinary presence of mind and superb common sense.

It is, of course, an usual practice to have a *chemical laboratory* directly under the command and supervision of a senior cadre laboratory technical personnel who should be consulted, as and when required, for his expert opinion and advice. It is, however, pertinent to mention here that **two** vital universal truths and norms, namely : *first,* exercise of utmost care ; and *secondly,* adoption of strict safe-working procedures, should be the prime responsibility of each and every individual working in a chemistry laboratory. No compromise, whatsoever, must be made with regard to even an iota of doubt as to the safety of a proposed experimental procedure yet to be undertaken. Liberal consultation, advice from senior research personnels, academic supervisors should be sought freely and frankly without the slightest hesitation in one's mind.

Genuinely speaking, everybody should not only adopt but also execute an extremely high sense of responsible attitude towards their work. There is absolutely no scope of any sort of hurried behaviour, short-cut procedures, thoughtless or ignorant line-of-action that may end-up with an accident and most probable harm caused to themselves and others too. They must be fully aware of what is going on elsewhere or around them in the same laboratory set-up ; and be fully conversant of the possible hazards taking place either ensuing from their own experiments or arising from others.

It has been observed beyond any reasonable doubt that most of the unfortunate accidents in a chemical laboratory invariably occurs on account of such glaring facts, namely : to achieve results in the quickest possible time-frame, to ignore knowingly certain already familiar and

prohibited short-cut method(s), and lastly to work half-heartedly and carelessly in a laboratory. Therefore, one must abide by the **Golden Rules** to maintain and create the safest environment in a *chemical laboratory,* such as : to work carefully, methodically, painstakingly, thoughtfully, diligently and above all whole-heartedly.

In short, it may be summarized that an unplanned event causing damage or injury to oneself, otherwise termed as an '*accident',* in a **chemical laboratory** can be avoided to a bear-minimum-level, if not cent-per-cent, by adopting all safety norms and procedures besides working with a '*cool mind*' and a '*smile'* on the face.

1.2 GUARD AGAINST PERSONAL SAFETY

A *'research chemist'* must ensure that he/she is not subjected to any sort of risk or danger against his/her personal safety, at any cost, while working in a **chemical laboratory.**

1.2.1 Protective Coat

Each and every person working in a *chemical laboratory* should put on a full-length and full-sleeve protective coat, preferably white, because any type of stains and inadvertent spillages are more apparently visible and detected vividly.

1.2.2 Protection for Eyes

The human eye is probably the most vital sense-organ, and obviously the most delicate due to its fragility. Therefore, the protection for eyes is of top-priority with regard to several possible eye-hazards, namely : exposure to the dust of fine chemicals, fumes or vapours, sudden splashing of liquid chemicals (hot or cold) and even from splinters of glass wares that get exploded while performing an experiment. In order to avoid such untoward and unpredictable possible hazards in a *chemical laboratory* the use of a pair of **safety glasses** should be mandatory. There are a plethora of superb quality, pretested, certified, light-weight spectacles and goggles abundantly available from various reputed laboratory suppliers. These eye protective guards do provide in routine use the necessary required good coverage of the eyes and also the upper face. Of course, there are several models and designs that are quite suitable for use upon the prescription glasses.

Nevertheless, **prescription safety glasses,** that are made-to-order, are readily available through specialized sources only, and though a little more expensive, should be used exclusively for the full-time laboratory researcher or staff. It has been observed that the *contact lenses* do provide certain extent of protection against possible mechanical damage to the eye ; however, the wearing of protective goggles is still very much essential and almost a must.

It is pertinent to mention here that either the usage of **close-fitting-safety spectacles** or, preferably, a **vison covering the entire face** may provide a much enhanced level of protection in the event of chemical splashing or spraying of corrosive or toxic hot liquids or gases.

Importantly, while carrying out experiments that are either suspected to be *explosive* or *hazardous* in nature, additional protection afforded by **safety-screens** is vehemently recommended.

Fume-Cupboards. All experiments involving toxic solvents and reagents should be carried out in an efficient fume-cupboard provided with a heavy-duty chemical protected exhaust system.

Disposable Plastic Gloves. Good quality disposable plastic gloves must be used profusely while handling both corrosive and poisonous chemicals.

1.2.3 Conduct in a Chemistry Laboratory

The overall conduct in a **'chemical laboratory'** should be associated with dignity, discipline, maturity, poised behaviour, cool temperament, charged with excellent presence of mind and above all a soft-spoken pleasant disposition. It is, however, absolutely necessary to invoke a high degree of self-discipline with regard to the following cardinal aspects, namely :

- Over-hurried activity
- Smoking
- Eating and drinking
- Irresponsible behaviour (or practical jokes)
- Shouting and screaming.

Over-hurried activity particularly in a **chemical laboratory** may tantamount to serious mishaps thereby causing both intensive and extensive damage/injury to oneself, others and also the laboratory as such.

Smoking is strictly prohibited in a **chemical laboratory for** obvious reasons that invariably the organic solvent or their fumes are **highly inflammable.**

Eating and drinking in a **chemical laboratory** should be forbidden so as to avoid the possible risk of ingestion of toxic substances either directly or indirectly.

Irresponsible behaviour (or *practical jokes*) must not be allowed while working in a **chemical laboratory** so as to maintain both santity and a congeneal atmosphere amongst the colleagues of either sex.

Shouting and screaming may be avoided, as far as possible to distract someone's concentration or attention unduly that may perhaps cause personal distress or pain totally uncalled for.

1.2.4 Neatness and Cleanliness

It is a well-known common addage that—'*next to godliness is cleanliness*'. A *chemical laboratory* must maintain a high degree of neatness and cleanliness that may indirectly contribute as a major factor in laboratory safety. Passageways either around the working benches or in-between them should not be made untidy by litter rather these are to be thrown into a metallic-covered-dustbin kept in one corner of the laboratory. The top of the working bench always be kept neat and tidy and avoid scattering with apparatus not-in-use. All such apparatus should be stored in the cup-board beneath the bench. Likewise, all dirty apparatus should be dipped in either a solution of a detergent or a cleansing-mixture in a plastic bowl a little away from the working area that may be cleaned and kept away for future usage as and when required.

Note. All solid and filter paper waste should not be thrown in the sink.

It is the prime responsibility of a '*good chemist*' to meticulously and scrupulously clean and subsequently drying of all used glasswares. For highly moisture-sensitive compounds the glasswares need to be rinsed with acetone, twice at least, dried in an oven and brought to ambient temperature in a desicator. It is indeed advisable to clean-up the used reaction flasks and other apparatus immediately after their usage so as to avoid tedious cleansing process later on.

It is pertinent to mention here that there exists not a single known **universal cleansing mixture**. Therefore, based on the *nature of the deposit* and *amount of the deposit* a *chemist* must undertake the process of cleaning accordingly in a systematic manner rather than adopting a haphazard style.

The various usual standard cleansing processes are stated below in a sequential manner ; namely :

(1) *For basic residues.* Dilute sulphuric acid or hydrochloric acid may dissolve the basic residues completely.

(2) *For acidic residues.* Dilute sodium hydroxide solution is probably the commonest and the best cleansing agent for most acidic residues.

Note : In (1) and (2) above cases the washings of basic and acidic aqueous solutions may be washed down the drain thoroughly with plenty of fresh water so that the drainage pipes are duly flushed out of the corrosive substances.

(3) *For organic solvent miscible residues.* In instances where the *stubborn* residues that are miscible only in comparatively cheaper solvents, may be used profusely and should be collected in the '*residues*' bottle and **not down the sink.** The combined residual organic solvent may be distilled off to recover the 'good' solvent and reject the heavily contaminated material appropriately.

(4) *Fro gross deposits.* The cheapest, best, and simplest means to get rid of gross deposits may be accomplished by employing commercial household washing powder containing an abrassive component that does not necessarily scratch the glass surfaces at all, such as : 'Rin', 'Vim', 'Ajax' etc,. The washing powder could be applied either directly into the apparatus previously moistened with water or using a test-tube cleaning brush that has been soaked into the powder ; the surface of the glass is subsequently scrubbed gently followed by vigorously until the sticking dirst has been removed entirely. Ultimately, the glass apparatus is washed and rinsed thoroughly with 'soft' tapwater.

Note : In the event when washing with a mixture of washing powder and water fails to give an entirely satisfactory results, the powder may be mixed with a polar organic solvent, for instance : acetone or iso-propanol.

Importantly, in case the above cited **four** cleansing methods do not offer hundred per cent satisfaction one may attempt any **one** of the following **three** vigorous and stringent '**alternative**' cleansing solutions, namely :

(*a*) **Trisodium Phosphate Solution [Na_3PO_4 ; 15% (w/v)].** A warm (30-40°C) solution of trisodium phosphate which has been mixed with a small quantum of an abrassive powder *e.g.*, *pumice powder.* However, this particular reagent is not suitable for the cleansing of either *tarry residues* or *sticky/gummy materials.*

(*b*) **Decon 90.** It is an extremely effective *surface-active-agent*, which is asserted to be practically able to take care of all laboratory cleansing operations. Besides, it also bears other remarkable characteristic features of the present day consumer acceptability requirements, namely : 100% biodegradable, almost non-toxic, phosphate-free, and totally rinsable. It has been widely recommended for the removal of various obstinate deposits, such as : *tars, polymeric residues, greases* and *silicone oils.*

(*c*) **'Chromic Acid' Cleaning Mixture.** It is considered to be one of the commonest, tried and tested cleansing mixture most abundantly employed in practically all **chemical laboratories** across the globe.

Preparation. The 'chromic-acid' cleansing mixture may be prepared conveniently from the following ingredients :

(*i*) Sodium dichromate : 5 g

(*ii*) Water : 5 ml

(*iii*) Sulphuric acid (36 N) : 100 ml.

First of all, 5 g of sodium dichromate are dissolved in 5 ml of water in a 250 ml pyrex glass beaker to which 100 ml of concentrated sulphuric acid are added in small lots at intervals with frequent stirring with a clean glass rod. Being an **exothermic reaction** the temperature will rise to 70–80°C initially, which may be allowed to fall down to 40°C over a span of time. The cooled cleansing mixture may be transferred to a clean, dry and labelled glass-stoppered bottle.

The glass apparatus to be cleaned must be rinsed with water to get rid of the water-soluble organic matter as far as possible along with the possible reducing agents, if any. Subsequently, the water is drained off from the apparatus to its maximum extent ; and the *'chromic acid' cleaning mixture* is introduced into it in a quantity just sufficient to smear the solid residue adequately, while the main quantum of the cleaning mixture returned to the stock bottle. The cleaning mixture treated apparatus is allowed to stand for about 15–20 minutes, with occasional swirling of the apparatus to stretch out the liquid onto the surface of the solid residue, the former is rinsed thoroughly with running tap water an finally with distilled water.

Note : It is advisable not to attempt any other 'chemical treatment' whatsoever due to the possible ensuing explosion hazards.

Ultrasonic* Bath. The use of *ultrasonic energy* to clean objects, including **medical** and **surgical instruments** is a very common practice in a hospital environment.

Importantly, such sophisticated techniques have also been exploited from a highly sensitive sterile-zone of an **'operation theatre'** in a hospital to the **'chemical laboratory'** for the benefit of *'research chemists'* as well.

The ultimate and final removal of '*trace residues*' from previously treated and cleaned glass apparatus may be accomplished by **ultrasonic bath** having various capacities ranging from 2.7 to 85 litres, and the tank fluid in **Decon 90.**

***Ultrasonic.** Pertaining to sounds of frequencies above approximately 20,000 cycles per second, which are inaudible to the human ear.

Note : It is important to **warn** here that all apparatus essentially *loaded with gross impurities* must **not** be cleaned in these high-tech baths for obvious reasons because the 'tank fluid' shall become profusely contaminated thereby minimising its overall efficiency to a significant extent.

Advantage. One of the major and most crucial functional utilities of **ultrasonic baths** is their excellent and remarkable ability to loosen difficult and rather stubborn ground-glass joints when these get 'fused' on account of degraded chemical contaminants or a prolonged neglet by an user.

Drying of Cleaned Laboratory Glasswares. There are, the fact, two different sizes of glass apparatus one invariably comes across in a **chemical laboratory,** for instance : (*a*) small ; and (*b*) large and bulky.

(*a*) **Small Apparatus.** These are thoroughly cleaned and rinsed with distilled water and kept in an electrically heated oven, preferably having an inside chamber and trays made up of stainless steel, previously maintained at 100—120°C for a duration of 60 minutes.

(*b*) **Large and Bulky Apparatus.** There are quite a few really large and bulky apparatus which fail to enter an oven for drying or sometimes needed soon after washing for urgent experimental operations. Therefore, other viable, effective and convenient means of drying such large and bulky apparatus have been devised duly, such as :

(*i*) In case, the apparatus is wet with water, the latter is removed to the maximum extent and subsequently rinsed with small quantity of either acetone or industrial spirit.

Note. For the sake of economising on solvents the aqueous acetone or industrial spirit are collected separately and stored in labelled 5 litre HDPE bottles for future recovery by distillation are re-cycled usage.

(*ii*) The final drying is afforded by the help of *Hot-Air-Blower** (supplied by Gallenkamp).

1.2.5 After-Hours Working

Dedicated and diligent '*research chemist*' may have to work late in the evening or in the night to complete the on-going reactions that invariably requires close supervision or monitoring. In such instances, it is absolutely necessary and a must that at least *two persons* should be physically present in a **chemical laboratory** particularly in after-hours working. Personal harmonious understanding amongst the chemists working in a laboratory is equally important and vital whereby one may look after simple operations, such as refluxing, evaporations on a water-bath, digestion, distillation, column chromatography, soxhlet extraction and the like. In such instances, clear written instructions must be communicated so that the other chemist can stop the experiment when it is either over or in an emergency.

1.2.6 Guidelines for Accident or Injury

Each and every individual working in a **chemical laboratory** must be fully aware about the location of the *fire escapes* and *exits ;* and also ensure that there is no obstacle or restrictions

*__Hot-Air-Blower.__ A sturdy, heavy duty power-driven blower that functions on a simple principle *i.e.,* it draws air through a filter, passes it through a heater, and forces it upwards through pointing tubes that hold the apparatus.

to them. It is also important that all chemists of either gender must know the exact positions of the **'Fire Extinguishers'***, fire-blankets, and drench showers, and should make sure how they are made operational. (**Caution :** *The checking of such equipment(s) should be carried out periodically and duly certified by the appropriate authorities.*)

Each *chemical laboratory* must-clearly display such available facilities at strategically located positions, namely : first-aid equipment, nearest telephone, emergency medical team(s), hospital(s), and fire brigade(s), so that in the event of an accident and immediate action is feasible.

Besides, all these gospel truths one should always exercise the utmost presence of mind in any accident big or small.

Burning Chemicals and Clothing. Accidental fire from highly inflammable organic solvents is observed to be one of the most common and equally dangerous fire hazards in a *chemical laboratory.* In case the fire is exclusively limited to a small vessel, such as : beaker or china-dish or flask then cover it instantly with an asbestos-wire-gauze so as to cut off the air containing oxygen to the burning solvent. Because, most of the inflammable organic solvents are actually having lesser density than water ; therefore, **water should never be employed to extinguish fire.** However, ordinary bucket-of-sand is invariably useful for *small fire incidents ;* and for comparatively *larger fire cases* a fire-extinguisher should be put into action. Of course, for fires beyond reasonable control, first the fire alarm must be triggered, and **immediately** the **fire-brigade** summoned without a second thought.

In such circumstances when one's clothes catch fire due to the splash of burning organic solvents, the victim should be immediately made to roll over on the ground to extinguish the fire or he/she must be covered instantly with a **fire-blanket.**

(**Note :** Any type of fire-extinguisher must not be used on a person).

Minor Injuries. Minor injuries on palm or fingers on either hands are usually inflicted due to sharp broken edges of laboratory glass tubings or glasswares. The exposed or cut should be thoroughly flushed under a running cold-water tap, excess water removed, applied with an antibiotic cream, and covered with a suitable bandage. In the event, when one receives a deep and serious cut, an immediate medical assistance must be sought for adequate specialized attention, such as : stitching (under local anaesthetic conditions), medication with an antiseptic cream, pain-killing tablets, and lastly an **anti-tetanus** toxoid injection**. Likewise, minor burns caused either by hot equipment or corrosive chemicals, *e.g.,* caustic, concentrated mineral acids, liquid bromine and the like, are observed to be a routine laboratory hazards. Simply flush out the excessive chemicals from the affected area with cold running water or sometimes even ice-cold water, and subsequently ask for due medical assistance.

1.2.7 Storage of Chemicals/Reagents in a Chemical Laboratory

All *'research chemists'* are required to use various types of chemicals and reagents as cautiously and carefully as possible, and subsequently return them to their properly designated cupboards,

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*__Fire Extinguisher.__ A device for discharging liquid chemicals or foam to extinguish a fire.

**__Tetanus.__ An acute infectious disease of the central nervous system caused by an exotoxin of the tetanus bacillus, *Clostridium tetani.*

shelves or chemical stores soonafter their use. It is pertinent to state here that chemicals, in general, should never be allowed to accumulate either in fume cupboards or on working benches so as to avoid possible uncalled for inconveniences that may ultimately lead to possible accidents or spillages.

Importantly, the following standard norms and regulations with regard to the storage of chemicals/reagents in a *chemical laboratory* should be observed rigidly and strictly :

(*i*) Bulky containers and bottles of dangerous and highly inflammable and corrosive chemicals must be returned to the main chemical store immediately which is governed exclusively by specific regulations for safe storage.

(*ii*) Each specific *chemical laboratory* is under strict regulations with regard to the storage of solvents, and that too in a specially designed fire-proof steel cabinet fitted with a vapour-seal door. Furthermore, such an area should be duly assigned and adequately equipped for the safe issue of toxic, corrosive and flammable solvents and reagents.

(*iii*) Transportation of innocuous or dangerous chemicals stored in properly capped Winchester bottles for a short distance must be **duly supported both at the base and at the neck, and never at only one of these critical places.** However, for longer distances the specially designed movable safety carriers that are commonly available must always be used.

(*iv*) *Hazard code* or *hazard symbol* should be positively imprinted on a container into which the chemical or reagent has been transferred from a bulk container. Besides, the **'label'** must essentially bear such informations as : nature of the contents, risk and safety summaries stating clearly the possible danger linked with the contents.

(*v*) **Proper Labelling of Reagents and Chemicals.** In a *chemical laboratory* all usable reagent bottles and chemicals must be labelled clearly and explicitely either with computerized labels, typed labels or neat hand-written labels. In such instances where the containers have lost their labels, their contents must be identified positively and relabelled accordingly ; should there be an iota of doubt, the material must be disposed of immediately and safely. It has been found frequently that the gummed labels peel off rapidly ; hence, it is always preferable to seal them to the bottle or container with a good quality adhesive tape. As there are good many chemicals that are found to deteriorate with age ; therefore, it is always better to inscribe on the label itself indicating the exact date of its manufacture.

1.2.8 Glass-ware

Any glass apparatus which has any sort of crack, chip, flaw or even dirty, after careful examination, must be rejected immediately. More so, even a minute hair-line crack in a glassware meant for use in an assembly under an evacuated system are absolutely dangerous and should be discarded promptly.

It is always desired and recommended that all cleaned glass apparatus **not-in-use** must not be allowed to accumulate on the working bench but should be stored away safely beneath the bench.

1.2.9 Waste Disposal

Waste disposal forms an important aspect of laboratory management and utility. The cardinal objective, however, remains that waste material should not be allowed to accumulate in the premises of a chemical laboratory. Adequate periodical arrangement must be strictly adhered to with regard to the replacement of filled bins with the empty ones. From the practical point of view it has become almost necessary to store different types waste materials in separate labelled covered metallic bins positioned at convenient locations within the four-walls of the laboratory, such as :

(*i*) For broken glassware,

(*ii*) For inflammable materials,

(*iii*) For toxic chemical solids,

(*iv*) For waste solvents, and

(*v*) Innocuous waste solids.

All types of broken glasswares exclusively should be thrown into a covered metallic bin.

A lot of inflammable materials, for instance : paper, empty cartons, soiled tissue-papers, cloth pieces that may have been used to clean up inflammable liquids, used pieces of sponge, urethane-foam used as packing materials, used filter papers, empty card-board boxes, discarded rubber-tubings, plastic bags, cotton etc., must be stored into a separate bin.

Toxic solid wastes should first be stored into a disposable thick plastic bags, sealed properly and then stored into a labelled dust bin.

A lot of organic solvents are used in substantial quantum, and most of them are miscible with water and are highly inflammable. These should not be thrown into the sink but should be collected separately in different labelled containers. It is always advisable and also economical to redistill such solvents *e.g.,* acetone, ethanol, benzene, methanol, ethyl acetate etc., for reuse as cleansing purposes only. However, the waste acids and alkalies must-be first neutralized and then poured down the sink followed by liberal flushing with tap water*.

Innocuous (*i.e.,* harmless) waste solids *e.g.,* paper, filter paper,, cotton, tissue paper, blotting paper, used chromatographic paper, waxed paper, torn labels, file covers, brown-wrapping paper etc., must be stored separately into a labelled and covered metallic bin.

1.2.10 An Ideal Chemistry Laboratory

A modern well-equipped and ideal chemistry laboratory should be provided with the following additional requirements, besides the ones mentioned in various sections 2.1 through 2.9, such as :

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*According to **'Aldrich Catalogue of Fine Chemicals' :** the regulations in Great Britain with regard to the disposal of chemicals down the main drains are extremely stringent : **under no circumstances** should untreated wastes and water-insoluble organic solvents be thrown down the sink.

(*a*) **Smoke Alarm.** To detect the possible out-break of fire in the laboratory due to electrical short-circuit or smoke caused due to minor/serious chemical explosions generating thick and copious smoke.

(*b*) **Fire Alarm.** In case of emergency and violent fire accidents in the laboratory.

(*c*) **Fire Extinguishers.** Properly checked, functional and certified fire-extinguishers must be installed in the laboratory at strategic and easily accessible positions. These should be of dry-gas type and wet-foam type.

(*d*) **Exhaust-Fans.** Adequate, heavy duty exhaust fans must be fitted into each *chemical laboratory* to expel its atmosphere of the accumulated vapours of solvents, pungent odour of chemicals and other obnoxious fumes. They also create a natural *drift of fresh air* into the laboratory where several research chemists work at the same time for hours together. In this way, the human lungs get the scope of inhaling oxygenated air rather than the unwanted fumes and vapours of toxic chemicals.

(*e*) **Drench Showers.** Each *chemical laboratory* must be fitted with drench showers that may be useful in case of spillage of corrosive or harmful chemical(s) over the body of a person.

(*f*) **Fume Cupboards.** Provision of at least two effective fume cupboards must be made available in a *chemical laboratory* so as to enable the chemists perform all such reactions that evolve toxic gases, fumes or vapours. Even the chemicals to be poured, transferred or used in a particular reaction must be done in a fume cupboard for obvious reasons.

(*g*) **Telephone or Mobile Facilities.** At least two such communication devices must be provided in a laboratory so that in an emergency one may seek help for immediate intervention either for **medical help** or **fire-brigade services** round the clock.

1.2.11 Toxicity and Hazards of Chemicals/Reagents

A human being handles chemicals directly or indirectly, in one form or the other, whether it is in the **chemical laboratory** or in the house or contracted from a contaminated atmosphere. Invariably, a large number of chemicals are not only hazardous in nature but also toxic potentially. Toxicity usually refers to the inherrent property of a substance to cause injury on reaching either in an organism or a susceptible site. Innumerable chemical substances that one normally happens to come across in a laboratory may produce undesirable harmful effects by inhalation, ingestion or absorption through the skin. In the light of the above stark naked reality about the wide spectrum of chemical substances known till date one must handle them with utmost care and precaution so as to avoid any possible threat to one's health in particular and one's life in general.

The hazardous characteristic properties and their consequent effects on the human body of certain commonly used chemicals are summarized in the following table :

Characteristic Features of some Hazardous Chemicals

S.No.	*Name*	*TLV* (ppm)*	*Physical Characteristics*	*Harmful Effect(s)*	*Precautions*
1.	Acetaldehyde	200	Gas at RT**, bp 21°C ; Flammable ;	Inhalation of its vapours causes irritation to eyes, skin and lungs.	To be stored in a cool place.
2.	Acetic Anhydride	5	Liquid, bp 139.9°C ; pungent odour ;	Irritates eyes, skin, mucous membrane and causes nausea, vomitting.	To be used in a Fume-Cupboard.
3.	Acetonitrile	40	Colourless liquid ; bp 81.6°C ; Flammable ;	produces acute headache, nausea and dizziness when inhaled.	To be handled in a Fume-Cupboard.
4.	Acrolein	0.1	Colourless, flammable, pungent liquid, bp 59.7°C ;	Vapours cause severe lachrymal secretion and irritation to eyes.	To be handled in a Fume-Cupboard.
5.	Ammonia	50	Colourless gas ; bp – 33.5°C ; Pungent irritating odour.	Inhalation may cause suffocation, nausea, bronchitis, and pulmonary oedema.	To be handled in a Fume-Cupboard.
6.	Aniline	5	Colourless oily liquid ; Darkens in air ;	Causes nausea, dizziness and abdominal pain.	To be handled in a Fume-Cupboard.
7.	Benzene	10	Colourless liquid ; bp 80°C ; highly flammable.	Causes euphoria, headache and narcosis.	To be handled in a Fume-Cupboard.
8.	Bromine	0.1	Dark reddish-brown liquid ; bp 58.8°C ; rapidly vapourizes at RT.	Fumes are very irritating to skin, eyes, mucous membranes ; causes severe skin-burns.	To be stored in dark cool place.
9.	*n*-Butanol	100	Colourless liquid ; bp 117°C ;	Inhalation causes dizziness, paralysis, and respiratory inflammation.	To be handled in a Fume-Cupboard.
10.	Carbon Disulphide	20	Colourless or light yellow liquid ; bp 46°C ; inflammable.	Causes headache, vomitting and abdominal pain.	To be handled in a Fume-Cupboard.
11.	Carbon Tetrachloride	10	Colourless, non-flammable heavy liquid ; bp 77°C ; sweet odour	Causes irritation to eyes, headache, abdominal cramps, nervousness.	To be handled in a Fume-Cupboard.

* TLV = Threshold limit value (expressed as ppm or mgm^{-3})

** RT = Room temperature

S.No.	*Name*	*TLV* (ppm)*	*Physical Characteristics*	*Harmful Effect(s)*	*Precautions*
12.	Chlorine	1	Greenish-yellow gas ; suffocating odour.	Inhalation causes irritation to eyes, cough, pain, nausea, cyanosis and difficulty in breathing.	To be handled in a well-ventilated area.
13.	Chloroform	50	Colourless heavy sweet-smelling liquid ; bp 61°C. Non-combustible.	Causes unconsciousness, vomitting, and shortness of breath.	To be handled in a Fume-Cupboard.
14.	Diethyl Ether	400	Colourless, very volatile flammable liquid ; bp 34.5°C.	Inhalation causes headache, vomitting, paralysis and irritation of respiratory tract.	To be stored in a cool place.
15.	1, 2-Dichloro ethane	50	Colourless oily liquid having odour similar to chloroform ; bp 83°C. Slightly water soluble and flammable.	Causes irritation of respiratory tract, weakness, anxiety, headache and convulsions.	To be handled in a well-ventilated area.
16.	Formalin	3	Colourless gas with pungent odour ; highly reactive.	Causes corneal burns, dermititis, and conjunctivitis.	To be handled in a fume cupboard.
17.	Hydrazine	1	Colourless fuming liquid ; bp 113.5°C ; ammoniacal odour ; Possesses high fire and explosion risk.	Causes irritation of skin and tracheal tract, nausea and conjunctivitis.	To be handled in a Fuming cupboard.
18.	Hydroxylamine	—	Obtained as large white flakes ; mp 33°C. Highly unstable and hygroscopic.	Causes dizziness, headache, dispnea (breathing problem) ; jaundice and vomiting.	To be handled in a fuming cupboard.
19.	Iodine	—	Forms, greyish black plates or granules, mp 113.5°C. Soluble in ethanol, ether, chloroform and carbon disulphide.	Causes dizziness, headache, cough, breathing difficulty, and pulmonary oedema.	To be handled in a fuming cupboard.

S.No.	*Name*	*TLV* (ppm)*	*Physical Characteristics*	*Harmful Effect(s)*	*Precautions*
20.	Mercury	0.1 mg/m^3	Silvery and heavy liquid ; low vapour pressure (0.0012 mm/20°C)	Accidental swallowing causes burning sensation in the mouth, throat, nausea and thirst, followed by bloody diarrhoea.	To be handled in a Furming cupboard.
21.	Phenol	5	White crystalline mass but turns pink on exposure to air ; bp 182°C. Absorbs moisture from air and gets liquified.	Causes burns in mouth, pharynx, vomiting, cough and pulmonary oedema.	To be handled very carefully.
22.	Phosphorus Pentachloride	1 mg/m^3	Yellow powder, sublimes at 160–165°C without melting ; flammable.	Causes irritation to eyes, bronchitis, nephritis (*i.e.,* inflammation of kidney,	To be handled in a Fuming cupboard.
23.	Pyridine	5	Colourless liquid ; flammable with characteristic nauseating odour, bp 115°C ;	Causes puritis (itching), eczema, headache, vomitting, conjunctivitis, and abdominal pain.	To be handled in a Fuming cupboard.
24.	Thionyl Chloride	5	Pale yellow pungent liquid ; bp 79°C ; decomposed by water.	Causes conjunctivitis, dermatitis (skin inflammation), and pneumonia.	To be handled in a Fuming cupboard.
25.	Toluene	200	Colourless, inflammable liquid, bp 110.6°C ; freely miscible with ether ; ethanol, chloroform, and acetone.	Causes dermatitis, nausea, weakness, and incoordination.	To be handled in a Fuming cupboard.

RECOMMENDED READINGS

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13. MJ Pitt and E Pitt, **'Handbook of Laboratory Waste Disposal',** Wiley, New York, 1985.
14. DA Pipitone, **'Safe Storage of Laboratory Chemicals',** Wiley, New York, 1984.
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CHAPTER 2

Drug Synthesis

2.1. INTRODUCTION

The prime objective of this book is not only to focus emphatically the multifarious and varied aspects of **'practical medicinal chemistry'** with which a pharmacy professional student will need to be familiarized, but also get exposed and acquainted with the synthesis of important *'medicinal compounds'*. Drug synthesis may be accomplished by the actual preparation of a wide variety of compounds involving a representative careful selection of typical documented reaction processes and latest techniques. Perhaps, logically and justifiably the prospective budding *'medicinal chemists'* on the strong foot-hold of good theoretical knowledge and the various chemical, physical and spectroscopical aspects may begin to understand more vividly and explicitely the cardinal factors that essentially attribute their reactivity *vis-a-vis* biological activity.

'Drug design' or 'tailor-made compound' particularly aims at developing a drug with a very high degree of chemotherapeutic index and specificity of action. With the advent of latest concepts and tools evolved in 'Computer Aided Drug Design (CADD)' one may logically design a new drug molecule on as much a rational basis as possible.

It is, however, pertinent to mention here that 'medicinal chemists' have traditionally adopted synthesis as the **ultimate-concrete-evidence** of molecular structure(s) of natural products meticulously isolated from plant and animal sources. Over the years it has been universally accepted as an authentic and genuine *proof-of-identity* between an isolated natural substance and the compound produced by total-synthesis eventually confirmed the molecular structure arrived at through various physico chemical methods of analysis.

Therefore, a thorough basic concept and knowledge of *'drug synthesis'* may ultimately help a medicinal chemist to produce life-saving drugs, such as : penicillin, quinine, prostaglandins, steroids, anti-neoplastic agents. In short, synthetic medicinal chemistry, with the skill, wisdom and effort, has proved to be a major endeavor not only confined to the laboratories of Universities in general, but also to the bulk-drug industry in particular.

2.2. CONCEPTUALIZATION OF A SYNTHESIS

In the past one century and a half **'research chemists'** across the globe have evolved an innumerable, viable and potential synthetic routes for the preparation of any conceptualized **'target-drug-molecule'**. Interestingly, in the last four decades or so the very emergence of

the creation of piecing together a logical-philosophy and a well-conceived theoretical design have, in fact, made the entire task of complicated and strategic *'drug-design'* into a rather easier and viable proposition.

With the advent of computer-assisted-drug-design (CADD)* the overall cost of drug development may, therefore, be reduced drastically by minimizing the number of **drug candidates** that are synthesized and screened biologically enroute to each successful or computerized-molecular-modelling based 'target-drug molecules'. The computerized molecular graphics allow a research chemist to make optimum utilization of the ability of a computer-soft-ware to quantify an elaborated measurement of molecular geometry, conformation, electron densities, electrostatic potential energies and above all the direct comparisons of key structural feature of a wide range of biologically, potent active structure(s). The power of a human eye together with **'brain'** is able to interact directly and intimately with the data-processing capability of the computer.

There are a number of important considerations that have got to be followed sequentially, artistically, meticulously, and above all an individual's own skill and wisdom in accomplishing the '*target-drug-molecule'* as stated below :

(*i*) Prime considerations in designing synthesis,

(*ii*) The Synthon Approach,

(*iii*) The Retro-Synthetic Approach,

(*iv*) Materials required,

(*v*) Reaction specificity,

(*vi*) Purity and yield.

2.2.1 Prime Considerations in Designing Synthesis

The first and foremost objective is to conceptualize any given *'target-drug-molecule'* based theoretically upon pharmacophoric entities or various clues and indicators derived from biologically-active prototypes after a vigorous and thorough survey of a wide range of literatures available. Presently, any reasonably well-equipped library should have an easy access to on-line latest scientific journals and CD-Rom facilities so that a research chemist may reach to the bottom of the ocean of copious volumes of subject-related topics published in the world. From a close-look of the target-drug-molecule the researcher may logically ponder over the ways and means to accomplish their objective through the kinds of reaction(s) to make use in a sequential manner.

In other words, the strategic attack on the target-drug-molecule may be conveniently and formally divided into *two* major components, namely :

(*a*) **Basic Carbon Skeleton.** The importance of the basic carbon skeleton present in the conceived and proposed target-drug-molecule structure in any synthesis, cannot be ruled out. It may be accomplished through a series of reactions that eventually form the vital links to the newly proposed carbon skeleton. Therefore, the adequate planning on the board for the logical creation of carbon-carbon bonds, frequently

* O'Donnell, T.J. 'Uses of computer graphics in computer-assisted drug design, computer-aided drug design, methods and applications', Marcell Dekker Inc., New York, 1989.

termed as the **construction reactions**, is regarded as the backbone and obviously the most crucial step in designing a synthesis.

(*b*) **Inclusion of Functional Moieties.** Invariably, the necessary and required functional groups are most carefully and strategically positioned at various specific locations on the proposed target skeleton. These are usually dealt within a specific way, and hence could be the possible outcome of last reactions in the synthesis. They may also be carried out successfully either by means of aforesaid **construction reactions** or through **functional alteration reactions.** However, the latter operation(s) exclusively alter the *'functional moieties'* without affecting the basic carbon-carbon skeleton. The exact nature of the functional moieties present in the target-drug-molecule may, therefore, guide one precisely about what chemical reactions might be opted for.

In actual practice, one may also observe that a criterion of selecting organic reactions important in designing a synthesis is that the reactions usually occur at or adjacent C-atoms having the functional moieties. In other words, the very C-atoms which essentially bear functional moieties in the target shall normally also possess allied functions either in the starting products or intermediates of any synthetic sequence of reactions. Besides, it has also been observed that there are substantially very few reactions which might incorporate a functional moiety directly onto a hydrocarbon site located apart from another functional moiety ; and there are certain **construction reactions** wherein a functional moiety altogether vanishes from a C-atom. Bearing in mind the above vital observations and findings one may safely infer that—**"the location of the functional moieties present in target-drug-molecule structure is much more important than their actual nature".**

Summarily, there could be several genuine and possible reasons of undertaking the herculean-task for the total laboratory synthesis of an organic **target-drug-molecule** *ab initio* from simple precursors. Evidently, the pharmaceutical industry, looks for newer organic drug molecules that are particularly designed and synthesized with a possible hope that some of them may evolve as a potential useful **'new drug'** to combat the human sufferings and ailments. In short, the ultimate successful route of synthesis is indeed acclaimed as a highly creative and dedicated research output which is sometimes pronounced and described by such subjective terminologies as *beautiful* or *elegant* or *superb*.

2.2.2 The Synthon Approach

A **synthon** may be defined as—*'a structural unit that becomes an idealized fragment as a result of disconnection of a carbon-carbon or carbon-heteroatom bond in a retro synthetic step (transform)'.*

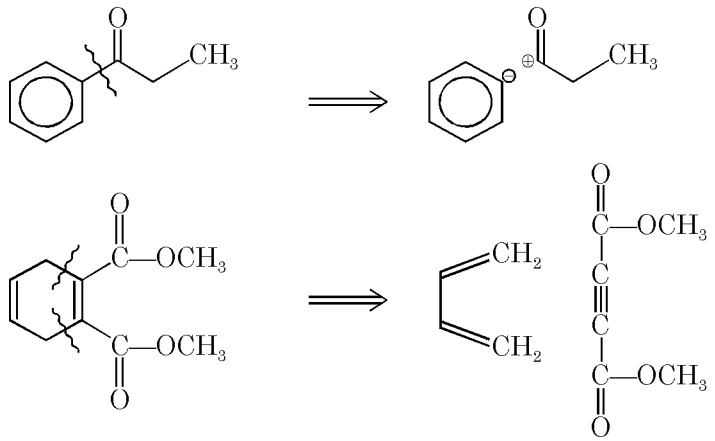
Therefore, one would broadly imagine that an open-chain structure while undergoing a single-disconnection step would ultimately yield **two synthons.** Further, an alike disconnection of a bond joining a functional group to a cyclic structure would also give rise to **two synthons.**

Interestingly, the *synthons* being obtained from single bond disconnections could be either **ions** (cations or anions) or **radicals** exclusively depending on the fact whether the cleavage encountered to the bond is heterolytic or homolytic. Invariably, they do not behave

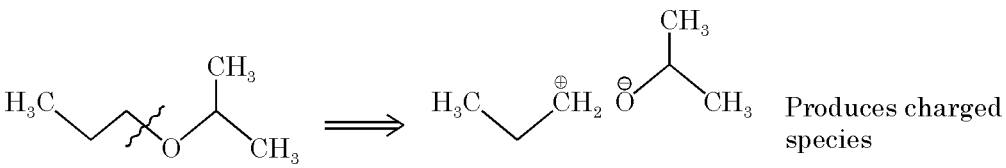
themselves as '*reagents',* but need to be connected to appropriate reactants that under suitable experimental conditions shall interact to cause the reverse, synthetic step. Nevertheless, synthons which are essentially 'neutral molecules' as such may be generated directly from *two* single-bond disconnections one after the other taking place in a **pericylic manner.**

A few typical examples are illustrated below :

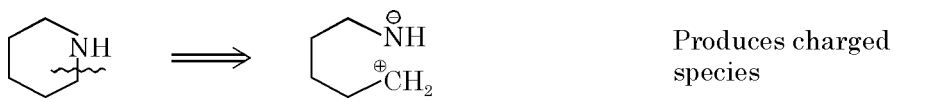
C—C Disconnections



C—X Disconnections



ALIPHATIC ETHER

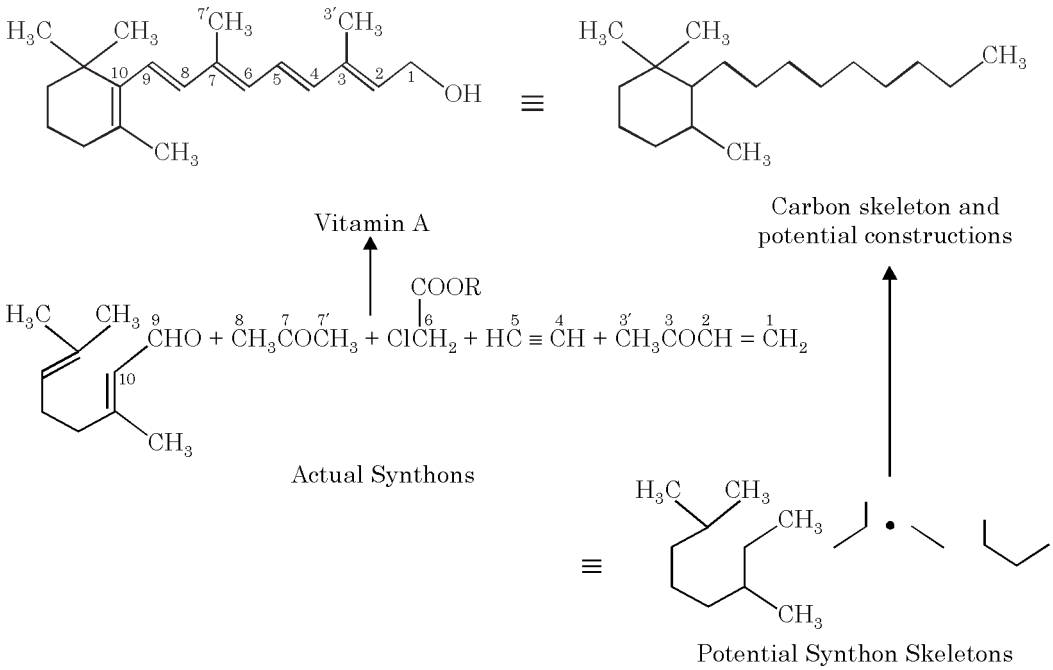


HETEROCYCLIC

2.2.3 The Retro-Synthetic Approach

In fact, the overall perspective and conception of a synthesis commences with a careful logical dissection of the target-drug-molecular skeleton into synthons. However, the disconnection of a bond within a monocyclic system shall be a *retro-synthetic ring-opening phenomenon,* otherwise termed as the **retro-synthetic approach.** Likewise, the disconnection of a bond caused in a bridged-structure would ultimately produce either a *mono-* or a *di-* substituted monocyclic structure. Sometimes, it may also be possible to accomplish two-bond disconnections taking place almost simultaneously.

A **double-line arrow** is invariably used to indicate a reaction written backwards—**the actual reaction in reverse.** The retro-synthetic approach may be expaliated with the help of the following classical example of vitamin A :



Salient Features. The various salient features of the retro-synthetic approach of vitamin A are, namely :

(1) Carbon-skeleton is dissected into various precursor components,

(2) Associated synthons are derived, and

(3) Dark bond-lines represent the probable location of the construction reactions.

2.2.4 Materials Required

A good, knowledgeable and academically competent research chemist is fully aware of the host of organic chemical reactions that are implied either directly or indirectly in designing synthesis. It is fairly understood and appreciated that common organic compound(s) and reagent(s) must be sourced through genuine and well-reputed manufactures round the world whose products are not only authentic but also cent-per-cent reliable and trustworthy, namely : Aldrich, Sigma, Fluka, BDH, Merck, Qualigens, Loba, and the like. Paradoxically, one may expect a, pure and reasonably good desired *'target-drug-molecule'* if and only when one makes use of **pure starting materials ;** of course, under rigid experimental conditions.

Salient Features of Materials. Following are some of the generalized salient features of starting materials, such as :

(1) Chemical compounds bearing simple-linear skeletons essentially having one to six carbon atoms and one functional moiety are available commonly. Such compounds generally give rise to certain basic organic entities, for instance : aldehydes, ketones, carboxylic acids and their derivatives, alcohols, and organohalogens.

(2) Cyclic compounds are available rather rarely and scarcely. However, compounds that are either five-membered or six-membered cyclic ones having a single functional moiety are available abundantly.

(3) Aromatic compounds that are available readily include : most of the benzene structural analogues having essentially either one or two functional groups attached ; besides, having side-chains consisting of upto 4 C-atoms with one functional moiety.

(4) Optically active chiral molecules that are available mostly belong to natural sources, namely : simple sugars, terpenes, and amino acids.

Broadly speaking, a research chemist profusely utilizes his wisdom and skill in designing the synthesis of rather complex natural products by employing relatively small synthons comprising of 1 to 5 C-atoms. In the event, when the *target-drug-molecule* contains a benzene ring, the selection of an aromatic starting material is invariably the best choice. In fact, the genuine demand of a chemist to have a relatively large starting-material molecule is fairly justified so as to minimise and cut-short the number of essential **construction-reactions ;** but unfortunately the quantum of such molecules are absolutely rare and scarce. It has also been a regular practice in designing a synthesis to make use of either naturally occurring starting material or an already synthesized chemical entity.

2.2.5 Reaction Specificity

It is an universal fact that a *target-drug-molecule* can be synthesized not by a particular mode of synthesis but also through several routes of synthetic methods. As the target molecules are not previously synthesized, therefore, one would not be able to predict which shall prove to be the **'best'** method of synthesis. Besides, a research chemist, with all the skills at his disposal, may also not be in a position to calculate in advance the overall nature of the various reactions involved *vis-a-vis* their yields of a variety of closely related as well as competitive routes of synthesis so as to profess or proclaim the **'best route'.**

Based on the actual realistic practical difficulties, with regard to the variable efficiency of synthetic methods and their corresponding yields, one may have to consider the following *three* important cardinal guiding principles that should be applied when choosing between alternate synthetic routes, namely :

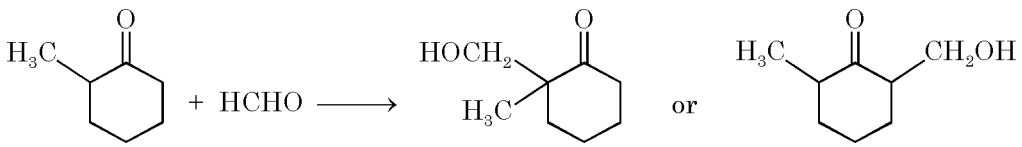
(*a*) An *'ideal synthesis'* must have a minimum number of steps involved.

(*b*) The reactions selected must have a good credibility with respect to their good record of reasonably high yields, and

(*c*) The ideal synthetic route selected must be squarely ascertained and critically examined so that other competing reactions, if any, are minimal. Nevertheless, competing reactions invariably aid in minimising the overall yield together with serious and cumbersome problems of separation.

Explanation for their principle. Let us consider an 'intermediate' from a chosen synthetic route which essentially bears two carbonyl functions ; and the subsequent step demands for a reaction involving one of the two carbonyl functions with a Grignard reagent. In order to accomplish a better efficiency of the reaction sequences one has to predetermine that out of the two carbonyl functions present which one would prove to be *'faster'* than the other.

Likewise, in the instance of a *Claisn condensation* or an *Aldol condensation* the role played by a **'ketone enolate'** has got to be pre-established as to which way the ketone function may prefer to enolize and finally react. However, their efficiency may not be alike.



2.2.6 Purity and Yield

In designing a synthesis usually a number of organic reactions are carefully opted out and performed in a sequential manner. In such a situation, when one is actively encountered with a set of synthesis routes, one may prevail upon the **'most-preferred-route'** that essentially has the least steps involved and makes use of the cheapest or the most easily available starting materials. Interestingly, to expect a 100 per cent yield in any organic reaction is nothing but a fairy-tale story or a day-dream. It has already been established beyond any reasonable doubt that in a *multi-step-reaction-sequence* the—**'overall yield is the mathematical product of the yields of all the individual reaction steps involved'.**

It has always been a practice to get the final or ultimate desired *target-drug-molecule* along with its various intermediates in its purest form achievable through chromatographic processes or recrystallization or distillation techniques. This aspect of highest purity of any compound synthesized in the laboratory is of utmost importance by virtue of the fact that the subsequent physico-chemical analysis data solely depends on it.

2.3. REACTION VARIANTS

The most vital and crucial aspect of **construction reactions** are essentially comprise of such reactions which help in developing the *basic carbon-carbon single bonds* (perhaps on which the rest of the '*pyramid*' is made subsequently). Therefore, such reactions primarily need a **carbon nucleophile** in order to make available the electrons for the bond formation ; besides, a **carbon electrophile** to accept them appropriately. In usual practice, the *nucleophiles* are typified by **carbanions** or their equivalent substitutes and also the π-bonds of **benzene rings** (aromatic) or **alkenes** (aliphatic). Likewise, the *electrophiles* are examplified by **electron-deficient carbon-atoms** commonly attributed by *three* types of entities, such as : *carbonyls ; conjugated carbonyls ;* and *C-atoms that rapidly become electron-deficient on being deprived of an attached functional group.*

It is quite evident that the various **functional moieties** play *three* major roles, namely : (*a*) initiating **construction reactions** ; (*b*) variation (alteration) of the functional moiety without causing any change in the basic C-skeleton, thereby altering the electronic-status of the region ; and (*c*) provide necessary **reactive centres** at which various reactions between synthons occur.

The reaction variants consist of a number of important aspects that shall now be discussed briefly in the sections that follow :

2.3.1 Structural Variants

A methodical, logical and scientific approach to the various ways and means to justifiably and usefully exploit and recognize the **structural variants** originally deduced from general organic reaction modes may be categorized under *two* heads, for instance :

(*a*) Nuecleophilic addition and substitution reaction patterns, and

(*b*) Electrophilic reaction patterns.

Consequently, these *two* distinct categories of reaction types may be summarized in the shape of tabular forms depicting the range of structures arrived at by specific nucleophile—electrophile combinations as given in Table-1 below. Thoughtfully, each side of the Table-1 may be regarded as a **half-reaction** belonging to either *oxidation-reduction* or *acid-base* chemistry.

However, in the same vein the various range of electrophilic reactions of unsaturated carbon-carbon bonds may also be summarized and illustrated as in Table-2. If one duly makes use of the contents of Table-1 and 2, loaded with a copious valuable and condensed informations, one should be benefited in *two* major aspects, namely :

(*a*) Recognition of structural variants in simplified fashion ; and

(*b*) Accomplishment of major reactions of synthesis through potential and judicious combinations of contents of Table-1 and 2.

Salient Features. Various salient features from Table-1 and 2 are :

(1) It is very much desired to select from the different boxes a wide range of such entities which are either very close in structure or readily convertible to, the probable functional moieties and structural types of **'target-drug-molecules'.**

(2) In this manner, the most suitable starting materials or intermediates to coin the desired 'target-drug-molecule may be deduced both logically and practically.

(3) Based on the evidences obtained from the abundant literature available on *'medicinal chemistry'* and *'organic synthesis'* besides the various clues obtainable from reaction mechanisms and their possible limitations a research chemist would readily apprehend and predict the course(s) of reactions which may ultimately **really work.**

2.3.2 Interchangeability of Functional Moiety

Though, it is a known fact that the **construction reactions** are the *pivotal crux* in designing synthesis of a target-drug-molecule, yet there are several other crucial factors that must be borne in mind before taking on the pre-planned operation(s). A few such important factors are, namely :

(*a*) Restricted utilization of such reactions that do not necessarily alter the basic carbon skeleton of the target molecule,

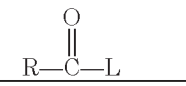
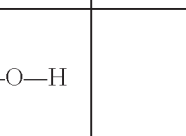
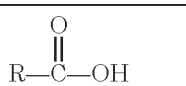
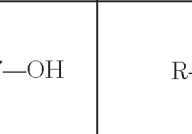
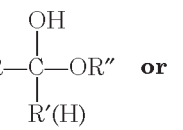
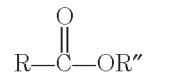
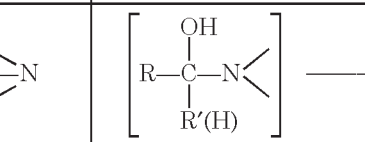
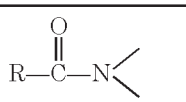
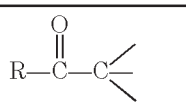
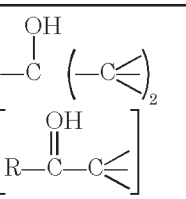
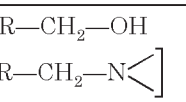
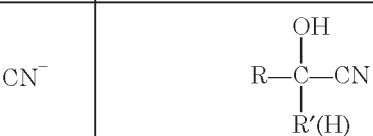
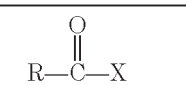
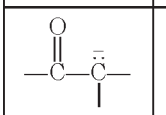
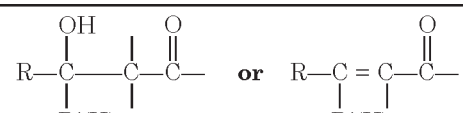
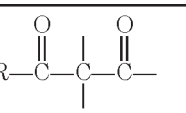
(*b*) Final outcome of **construction reaction(s)** may not yield the desired and correct functional moieties, but such entities must be interchanged to arrive at the *'target'*,

(*c*) Functional moieties obtained by one reaction at any particular *'intermediate stage'* may be altered in preparation for the next step of construction reaction, and

(*d*) The very initial and desired starting material may have to be obtained by affecting adequate changes in the functional moieties of available starting materials.

It has, however, been observed that interchangeability of functional moieties are invariably accomplished provided the basic carbon-skeleton remains unaltered.

Table 1. Nucleophilic Addition and Substitution Reaction Patterns.

ELECTROPHILIES			
			R—L
H—O—H			R—OH
R″—OH	 **or** 		R—OR″
			
		 [From Acids]	
		 [From Amides]	Generally not so important and usuful
H:⁻		 [From Amides]	R—H
:CN⁻		Generally not so important and useful	R—CN
X⁻	Generally not so important and useful		R—X
	 **or**		

R, R′ and R″ = Aliphatic groups ;
X = Haloatoms ;
L = Substituted functions ;

Table 2. Electrophilic Reaction Patterns.

Nucleophiles	ELECTROPHILES				
	Alkenes and Alkynes	Y_2 (Y = X*, H)	HY (Y = X, OH, OX)	—O—O—	:C<
	>C = C<	—C(Y)—C(Y)—	—C(H)—C(Y)—	—C(O)—C—	—C(C)—C—
	>C = C—C = C<	—C(Y)—C(Y)—C = C< —C(Y)—C = C(Y)—C—	—C(H)—C(Y)—C = C< —C(H)—C = C(Y)—C—	—C(O)—C—C = C< —C(O)—C—C(O)—C—	—C(C)—C—C = C< —C(C)—C—C(C)—C—
	—C ≡ C—	—C(Y) = C(Y)— Y—C(Y)—C(Y)—Y	—C(H) = C(Y)— H—C(Y)—C(Y)—Y	—	—C(C) = C—

.....(*Continued*)

Nucleo philes

Aromatics	X_2	HNO_3	H_2SO_4	$R-\overset{\overset{O}{\|}}{C}-L^{**}$	R—X
Z = N, O, S				R = Alkyl group	R = Alkyl group

*X = Br, Cl, I ; **L = Substituted Functions

Examples :

(*i*) Conversions of OH to *halides* and *tosylate,*

(*ii*) Interchangeability of —OH and $\rangle C = O$ by oxidation-reduction sequences,

(*iii*) Interconversions of COOH–*analogues* by hydrolysis to the corresponding acid, and subsequent conversion to another derivative,

(*iv*) Nitriles (CN) generated in construction reactions are easily convertible to the corresponding COOH moiety simply through hydrolysis,

(*v*) Reduction of nitriles (CN) may give rise to primary amines,

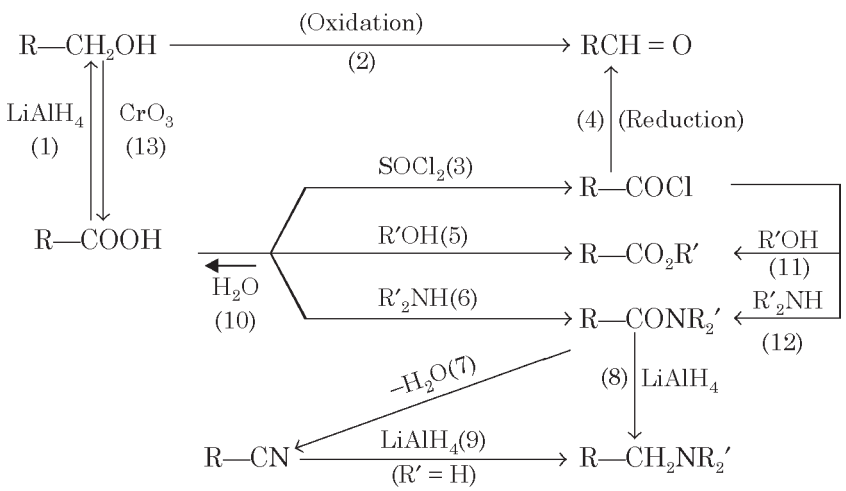
(*vi*) Primary and secondary amines are accomplished by reduction of amides ($—CONH_2$),

(*vii*) Aldehydes positioned at terminal C-atoms may be converted to acids by oxidation,

(*viii*) Primary alcohols situated at terminal C-atoms can be subjected to interconversion by reduction, and

(*ix*) Very specific reductive methods may be adopted to generate the much desired sensitive aldehydes at critical locations.

The following flow-chart summarizes the considerable interchangeability reactions of the **carboxylic acids** and other terminal functions :



$LiAlH_4$ = Lithium aluminium hydride ;

CrO_3 = Chromium 6-oxide;

$SOCl_2$ = Thionyl chloride ;

(Adapted from : *'Organic Chemistry',* S.H. Pine, McGraw Hill, Inc. New Delhi, 5th edn., 1987)

Salient Features. The salient features of the summarized interchangeability reactions of the carboxylic acids together with other terminal functions are as follows :

(1) Carboxylic acid on treatment with $LiAlH_4$ gives rise to a primary alcohol.

(2) Primary alcohol undergoes oxidation to yield the corresponding aliphatic aldehyde.

(3) Carboxylic acid when treated with thionyl chloride leads to an aliphatic acid chloride.

(4) The resulting aliphatic acid chloride on reduction produces an aldehyde.

(5) Carboxylic acid on treatment with a primary alcohol yields an ester.

(6) Carboxylic acid when treated with a secondary amine gives rise to an amide.

(7) Amide on dehydration produces a nitrile.

(8) Amide on being reduced with $LiAlH_4$ yields an aliphatic primary amine.

(9) Nitrile when reduced with $LiAlH_4$ also produces an aliphatic primary amine.

(10) Ester upon hydrolysis yields the parent carboxylic acid.

(11) Acid chloride on treatment with a primary aliphatic alcohol yields an ester.

(12) Acid chloride when treated with a secondary amine gives rise to the corresponding amide.

(13) Primary alcohol when oxidized with chromium-6-oxide yields the parent carboxylic acid.

Interestingly, one may observe from the above *flow-chart* that only **one functional group** (*i.e.,* carboxylic acid) along with its other terminal functions can afford **thirteen** interchangeable reactions. Thus, the research chemists wisdom, skill and expertise may ultimately make good the rather complicated job of designing the synthesis of a *target-drug molecule* into a lot easier task.

2.3.3 Selectivity in Reactions

It is, however, quite feasible and possible to affect change of one specific functional moiety without causing the slightest change to another, even when the two functional entities are almost alike. Such a situation may be accomplished very easily and conveniently as long as the two functional entities differ predominantly with regard to the **rates** for that *'specific reaction'*. It is, however, pertinent to mention here that there must prevail a difference of at least a factor of 10 that should specifically characterize the two rates of a particular reaction so as to enable one equivalent of reagent shall react almost negligibly with one group and practically 100% with the other. It has also been observed that a good number of *specific reactions* afford selectivity, as do a plethora of *reactant structures.*

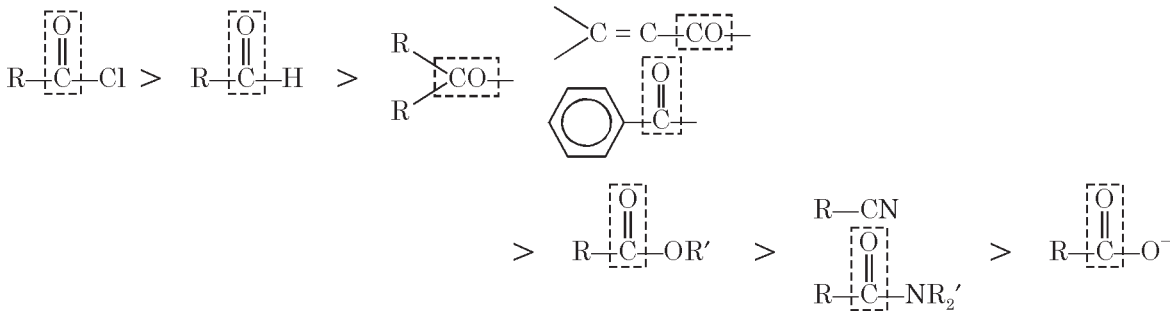
The various important and cardinal types of selectivity in reactions, as observed in organic synthesis, may be summarized as under :

A. Carbon-Carbon Double Bonds

Generally, the C—C double bonds are found to be almost unreactive to the nucleophiles unless and until these are duly conjugated with either carbonyl (—$\overset{\overset{O}{\|}}{C}$—) or other electron with drawing groups, such as : —NO_2 ; —CN ; —COOH ; —CHO ; —X ; —SO_3H ; —COR ; —N $(CH_3)_3^{\oplus}$

B. Carbonyl Groups

It has been observed that the order of reactivity of carbonyl-containing functional moieties with nucleophiles invariably decreases in the following order :



C. Catalytic Hydrogenation

Carbon-carbon double bonds (C = C), carbon-carbon triple bonds (C ≡ C), and nitriles (C ≡ N) may be subjected to hydrogenation without causing any affect to either carbonyl functions or aromatic nuclii by virtue of the fact that the reduction of the latter moieties is significantly much sluggish and appreciably slower. However, it is found that the reduction of triple bonds is comparatively faster than the corresponding double bonds ; and the on-going reaction may be arrested (stopped) at the double-bond stage by the aid of a **modified catalyst.** Lastly, the catalytic hydrogenation of the aromatic nuclii is normally extremely slow and sluggish.

D. Cyclic Reactions

It has been examined and observed that the cyclizations to produce *five*- and *six*-membered rings are significantly faster than their *intermolecular counterparts*. They are invariably favoured in equilibrium circumstances also.

E. Hydride Reductions

There are two commonly used reducing agents, namely : *first—sodium borohydride* ($NaBH_4$) which reduces exclusively aldehydes, ketones and acyl halides ; and *secondly—lithium aluminium hydride* ($LiAlH_4$) which reduces the above compounds as well as compounds belonging to the carboxylic acid family.

F. Saturated Carbons

The obvious differences in the reactivity of *primary, secondary,* and *tertiary* carbon atoms are normally quite satisfactory to explain their selectivity. Esterification of alcohols invariably adopts the same sequence *i.e.,* pri->sec->tert. In fact, the tertiary alcohols are generally quite unreactive with regard to the esterification.

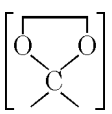
2.3.4 Protection of Functional Moieties

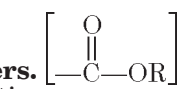
In designing the synthesis of a **target-drug-molecule** it is quite natural and also common that invariably more than one functional moiety is caused to participate in arriving at the various **'intermediates'** during the course of a synthesis. It is usually a common practice adopted by the research chemists to allow one particular moiety to function as the *reactive*

centre for one specific reaction ; whereas ; the other moieties are well *protected* for later purposes in the sequence of reactions. It is, however, pertinent to state here that one must ensure that the necessary conditions required for the desired reaction do not either interfere or lead to reaction at the other moieties.

Interestingly, a host of organic reactions are usually involved, having different specific experimental parameters, that do not eventually ensure **'reaction selectivity'** ; and under such critical situation(s) certain functional moieties need to be **protected** by first converting them into **'unreactive-structural-analogues'.** Hence, the protection of functional moieties may be accomplished by the help of a plethora of known organic reactions.

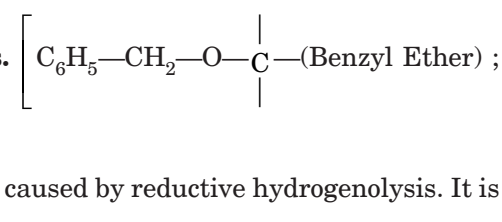
A few such examples are as given below :

(*a*) **Ketals.**  : are a common protecting group for carbonyl functions present in aldehydes and ketones.

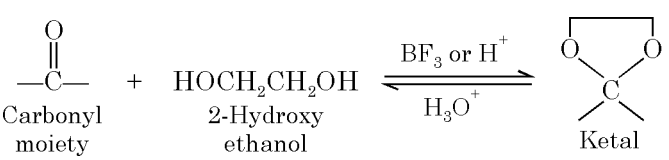
(*b*) **Esters.**  : are a common protecting group for carboxylic acid and alcohol functions.

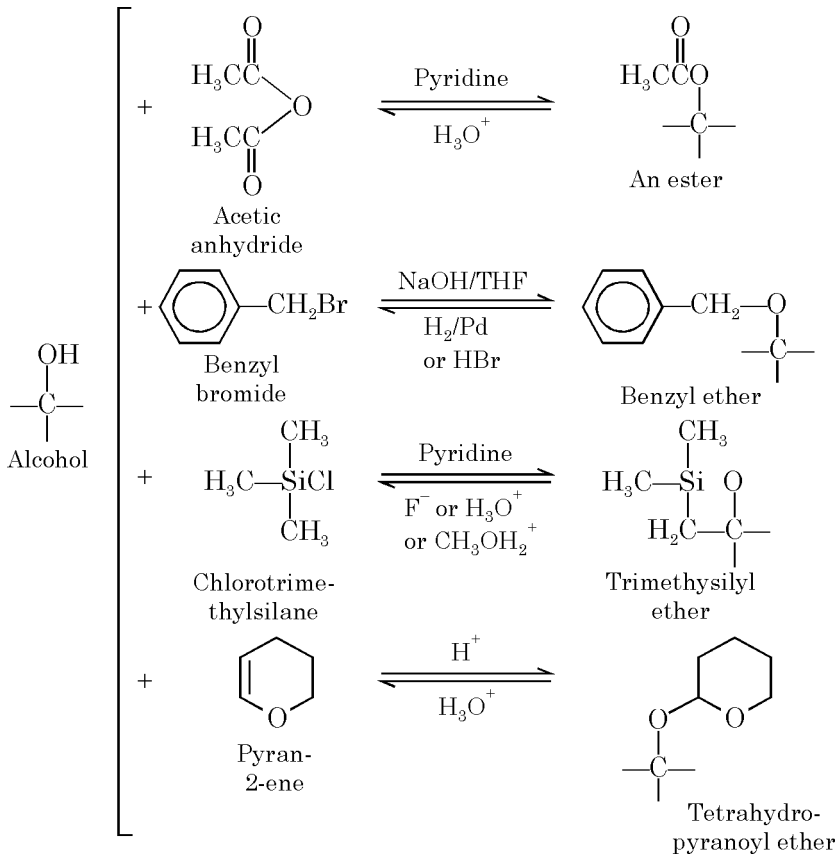
(*c*) **Ethers.** [—O—] : are a common protecting group for alcohols, such as : chlorotrimethyl silane [$(CH_3)_3$ SiCl] is at present frequently employed for protection of alcohols as **silyl ethers.**

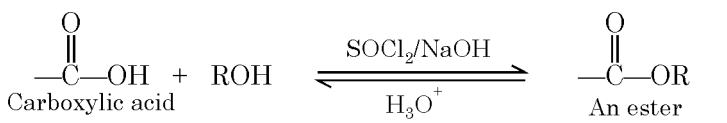
(*d*) **Benzyl Groups.** [C_6H_5—CH_2—] : are specifically employed for protecting alcohols and carboxylic acids.

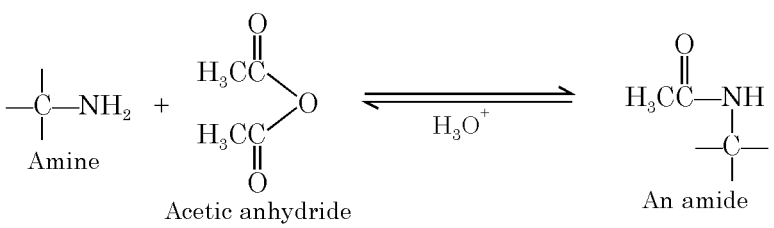
(*e*) **Cleavage of Benzyl Ethers and Esters.**  : are caused by reductive hydrogenolysis. It is pertinent to mention here that this specific reaction does not affect other ethers and esters.

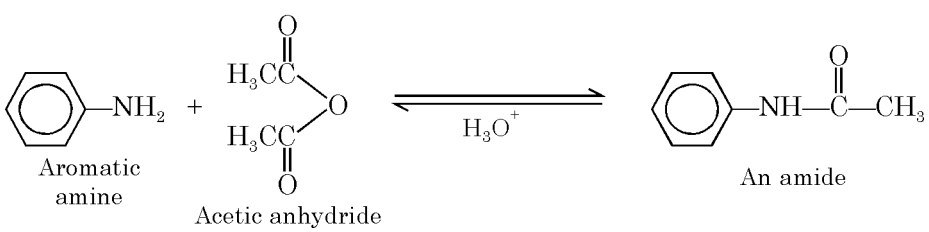
All the reactions pertaining to protection of functional moieties may be summarized as stated below :











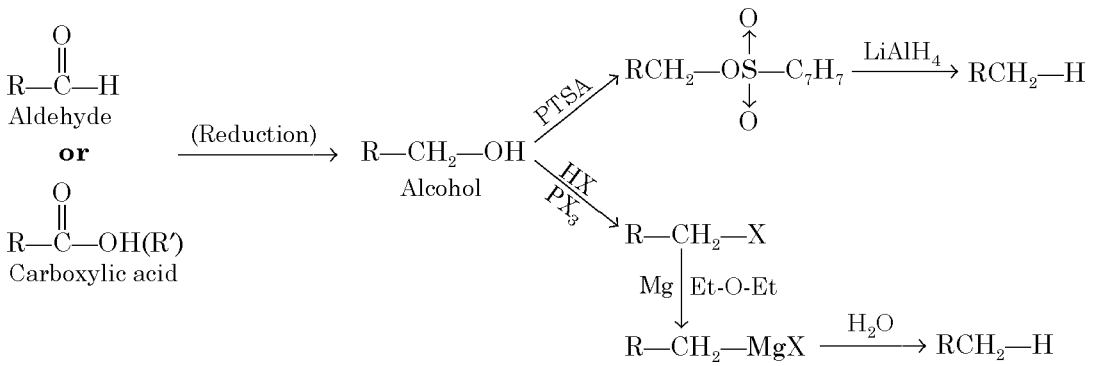
BF_3 = Boron Trifluoride ; THF = Tetrahydrofuran ;
$SOCl_2$ = Thionyl chloride ; $CH_3OH_2^+$ = Methanol onium ion ;
H_3O^+ = Hydronium ion ; Pd = Palladium ;

2.3.5 Elimination of Functional Moieties

From actual practice it has been observed that there are a good number of essential functional moieties which are required primarily to help in various construction reactions, but interestingly they do not appear in the **'target-drug-molecule'.** Therefore, it is extremely important and almost necessary synthetically to have adequate means and ways of eliminating such functional moieties completely.

A few such recognized practical ways through which the elimination of functional moieties could be afforded are as under :

(1) **Removal of carbonyl compounds *via.* hydroxy group.** It is quite evident that every compound containing a carbonyl $\left(\begin{array}{c}O\\\|\\-C-\end{array}\right)$ function, such as : an aldehyde $\left(\begin{array}{c}O\\\|\\-C-H\end{array}\right)$ or a ketone $\left(\begin{array}{c}O\\\|\\-C-\end{array}\right)$; and every member of the carboxylic acid family (R—COOH) is first of all converted to an alcohol (—OH) and subsequently to a C—H structure as given below :



PTSA = *para*—Toluene sulphonic Acid ;

$LiAlH_4$ = Lithium Aluminium Hydride ;

HX = Halo acid ;

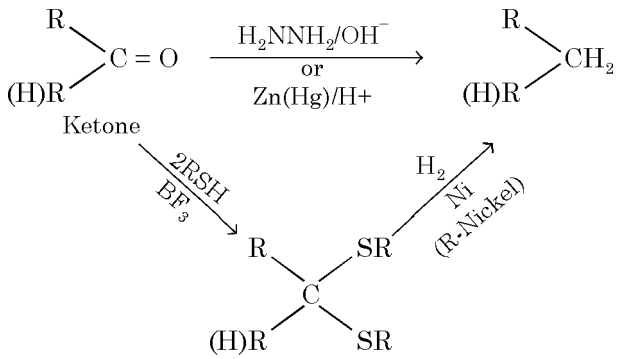
PX_3 = Phosphorus trihalide.

Explanation. An aldehyde or a carboxylic acid undergoes reduction to give rise to an **ALCOHOL.** The resulting alcohol finally yields RCH_2—H by *two* different ways, namely :

(*a*) By reduction with $LiAlH_4$, and

(*b*) By interaction with either HX or PX_3 into the corresponding alkyl halide which on further reaction with pure dry magnesium ribbon in diethyl ether generates the alkyl magnesium halide. The resulting product upon hydrolysis gives rise to the desired compound *i.e.,* R—CH_2—H.

Nevertheless, the alcohol (RCH_2—OH) on being treated with *para*-toluene sulphonic acid yields the corresponding *ester*.



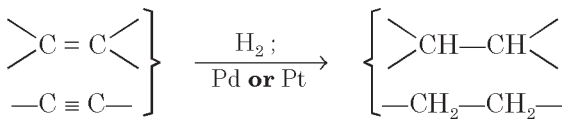
H_2NNH_2 = Hydrazine ; RSH = Thiol ;

Zn(Hg) = Zinc Amalgam ; BF_3 = Boron Trifluoride ;

R—Nickel = Raney Nickel (acts as catalyst in *'reduction'*).

Explanation. A ketone may be converted to R—CH_2—H in *two* ways : *first,* by treating with **hydrazine** in an **alkaline medium** ; and *secondly*, by treating with **zinc-amalgam** in an **acidic medium.** Ketone in the presence of 2 moles of an alkyl thiol and BF_3 gives rise to *an intermediate* which subsequently on reduction with Raney Nickel produces the desired product *i.e.,* R . CH_2—H.

(2) **Conversion of Alkenes and Alkynes to Saturated Hydro Carbons.** In usual practice, both alkenes and alkynes are easily converted to the corresponding saturated hydrocarbon functions by catalytic hydrogenation as shown below :



Explanation. The catalytic hydrogenation of alkenes and alkynes are afforded either in the presence of Palladium (Pd) or Platinum (Pt).

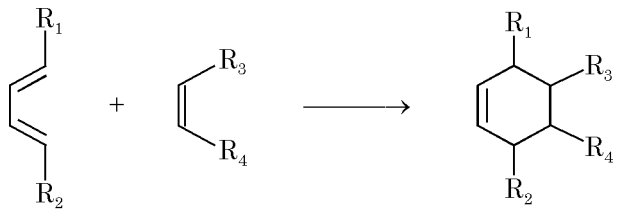
2.3.6 Annelation Reactions

A large number of **'target-drug-molecules'** invariably contain cyclic skeletons that could be either aromatic or heterocyclic in nature. Therefore, such specific reactions that help in the formation cyclic structures play a vital role in **synthetic medicinal chemistry.** These ring-forming reactions are usually referred to as **annelation reactions.**

It has already been established by means of experimental evidences that annealation reactions may be accomplished by a number of ways and means, such as :

(*a*) Reactions that essentially involve cyclization through intramolecular reaction of bifunctional compounds ;

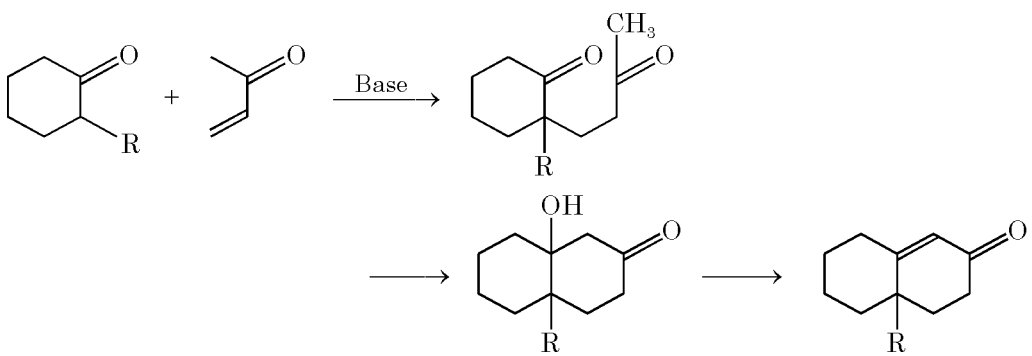
(*b*) *Diels-Alder Reaction.* It accomplishes both bond-making steps in a unique concerted, and regiospecific manner. In this reaction, the 1, 4-addition of the double bond of a dienophile to a conjugated diene to generate a six-membered ring, such that upto **four new stereocenters** may be created simultaneously. Thus, the [4 + 2] cyclo addition normally takes place with high regio- and stereo-selectivity :



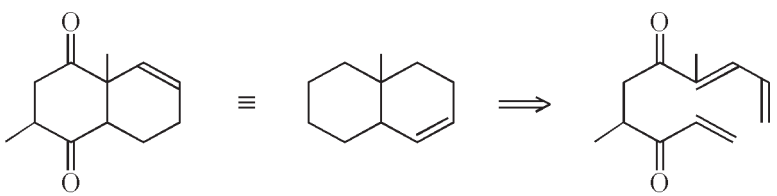
Diene Dienophile

It is, however, pertinent to mention here that the heteroatomic analogues of the diene (*e.g.,* CHR = CR—CR = O, O = CR—CR = O, and RN = CR—CR = NR) and dienophile (*e.g.,* RN = NR, R_2C = NR, and RN = O) may also serve as reactants.*

(*c*) **Robinson Annelation Reactions.**** It essentially accounts for the formation of 6-membered ring α, β-unsaturated ketones by the addition of cyclohexanones to methyl vinyl ketone (or simple derivatives of methyl vinyl ketone) or its equivalents, followed by an intramolecular aldol condensation as given below :



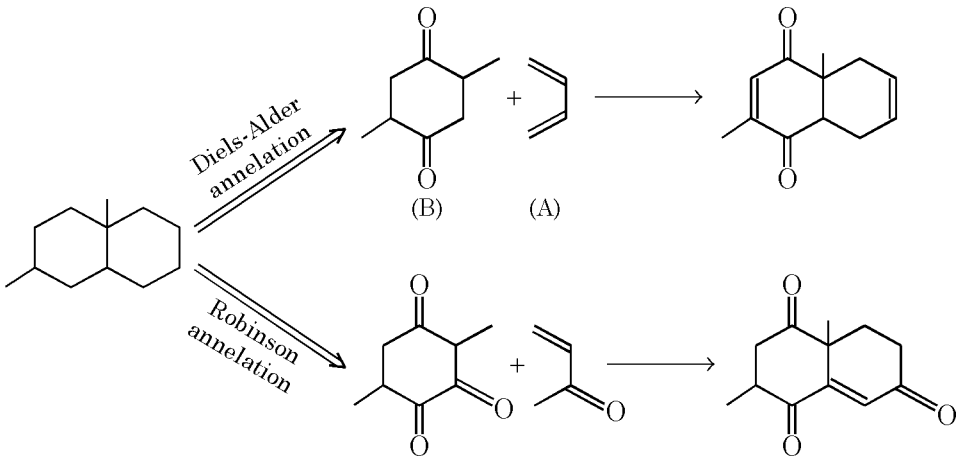
Let us assume a *target-drug-molecule* **A**, for which there are a number of possible annelation reactions of the *right-hand ring* as illustrated below :



A
(Target)

* T. Oh, M. Reilly, *Org. Prep. Proceed. Int. 26,* 131–158 (1994).

** W.S. Rapson, R. Robinson, *J. Chem. Soc.,* 1285, (1935).



First and foremost, a [4 + 2] **electrocyclic reaction**, is rejected outright by virtue of the fact that it is derived from a comparatively large synthon which may involve a number of steps to accomplish a **'construction reaction'.** The *second* possible prediction could be a *Diels-Alder Annealation* reaction ; and the *third* may be a *Robinson Annealation* reaction, both making use of rather *two* smaller synthons. Out of the last two probabilities, the former *i.e.,* Diels-Alder annealation reaction is chosen ultimately by virtue of *two* predominant facts, namely :

(*a*) It makes use of simpler starting materials *i.e.,* 1, 4-butadiene (A) and 1, 5-dimethyl-1, 4-benzene dione (B), and

(*b*) If offers a greater possibility of proceeding by the specified *regiochemistry*.

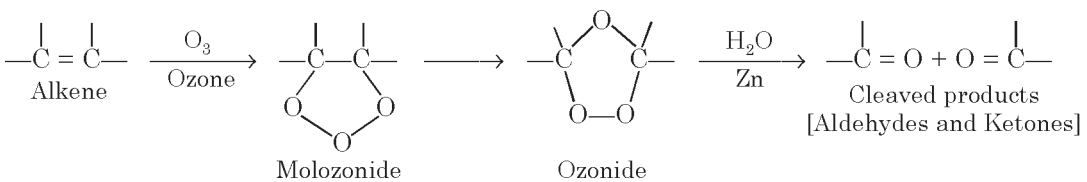
2.3.7 Fragmentation Reactions

It has already been discussed under section 2.1. (*a*) that *construction reactions* essentially establish carbon-carbon skeletons (bonds) in a **target-drug-molecules** ; those reactions that specifically cleave carbon-carbon skeletons (bonds) are usually termed as **'fragmentation reactions'.** In other words, the former enjoys its existence and importance to build up desired C—C skeletons and, therefore, are absolutely necessary in a synthesis ; however, the latter causes degradation or split-up of C—C skeletons and they also possess certain *vital synthetic utility*. There are, in fact, two important reactions that are particularly useful in affording the *fragmentation reactions,* such as :

(*i*) Ozonolysis, and (*ii*) Decarboxylation reaction.

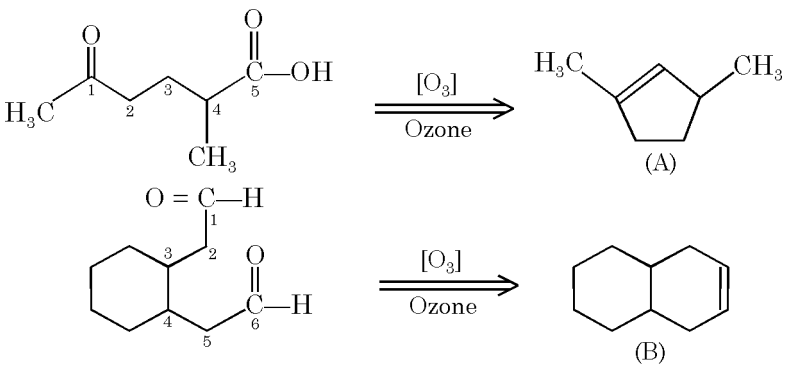
2.3.7.1 Ozonolysis. Ozonolysis (cleavage by ozone 'O_3') is accomplished in *two* stages, namely : *first,* addition of ozone to the double bond to form an *ozonide* ; and *secondly,* subsequent hydrolysis of the ozonide to produce the cleaved products.

Example. (1) Ozonolysis of **Alkene** to yield **Aldehydes** and **Ketones** :



Thus, the ozone gas is passed into a solution of the alkene in certain inert solvent like carbontetrachloride (CCl_4) ; evaporation of the solvent leaves the ozonide as a viscous oily substance. The resulting ozonide being highly unstable and **'explosive'** in nature, is **not** purified, but is made to react with water in the presence of Zn (a reducing agent) to obtain the corresponding *cleaved products*. Interestingly, in the resulting cleaved products—**a doubly bonded oxygen is found attached to each of the originally doubly bonded carbons (*i.e.,* aldehydes and ketones).**

(2) Ozonolysis of *Cyclopentene (A)* or *Cyclohexene (B)* to yield *target-drug-molecules* having **two carbonyl** $\left(\begin{array}{c}\mathbf{O}\\ \|\\ \mathbf{-C-}\end{array}\right)$ **functions** extended across 5 or 6 carbons apart :

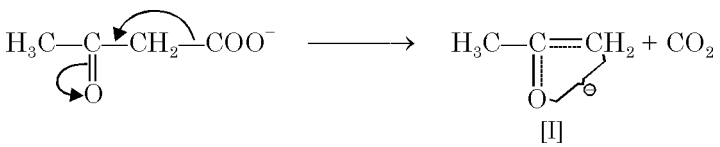


Cyclopentene (A) upon ozonolysis undergoes cleavage to give rise to an open-chain compound having carbonyl moieties at C-1 and C-5 positions ; whereas, *cyclohexene* (B) yields a cleaved product that bears the carbonyl functions at C-1 and C-6 respectively.

2.3.7.2 Decarboxylation. Decarboxylation, *i.e.,* elimination of the —COOH moiety as CO_2, is of restricted and limited utility for aromatic acids, and extremely important for certain β-**keto acids** and β-**diacids** (or substituted aliphatic acids : malonic acids).

Note. It is found to be absolutely useless for most simple aliphatic acids whereby it often yield a complicated mixture of hydrocarbons.

Decarboxylation of β-Keto Acids. It essentially involves both the *free acid* and the *carboxylate ion*. The loss of CO_2 from the corresponding anion gives rise to the **carbanion** [I] as shown below :



[I]

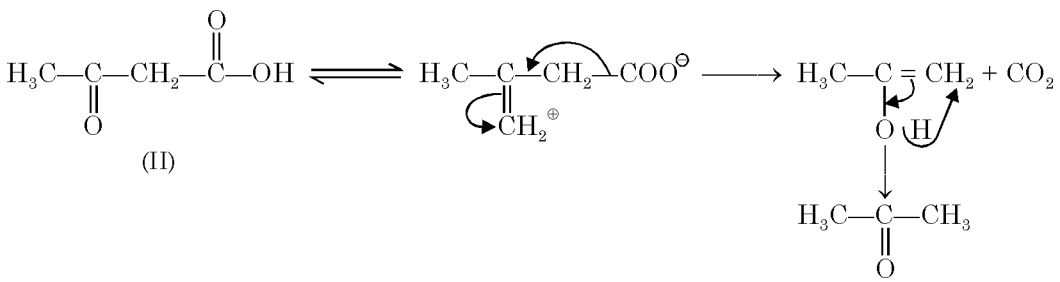
Explanation. The carbanion [I] is formed much faster than the rather simple carbanion (R : $^-$) which would be generated from a simple carboxylate ion ($RCOO^-$) because it is relatively more stable. Its greater stability is on account of the **accomodation of the negative charge** by the *keto function.*

Interestingly, the decarboxylation of **free acetoacetic acid (II)** specifically involves transfer of the acidic hydrogen to the corresponding keto $\left(\begin{array}{c}O\\ \|\\ -C-\end{array}\right)$ moiety in *two* manners, namely :

(*a*) *Prior to loss of* CO_2 *, and*

(*b*) *Simultaneously with loss of* CO_2,

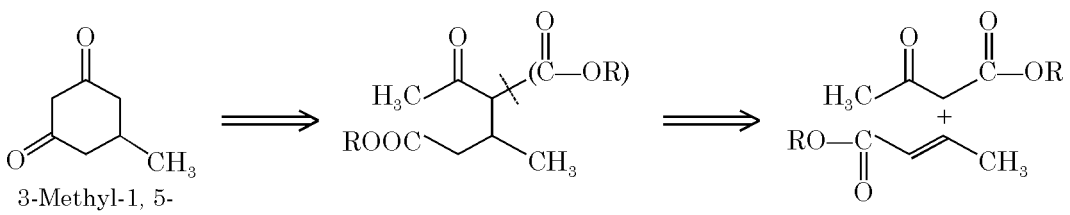
as illustrated below :



(II)

Note : It is known that the function of protonation is to minimise the basicity of a leaving group.

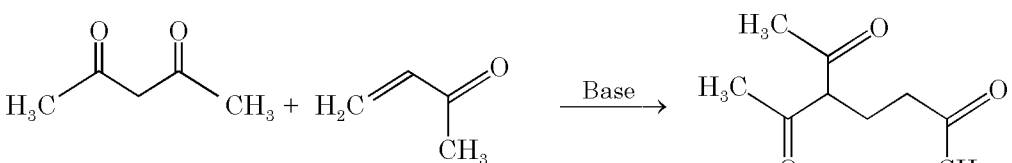
Example. Another important fragmentation reaction is the decarboxylation of (3-keto acids invariably employed for synthesis in conjunction with **construction reactions,** such as : Michael Reaction* (Addition, Condensation) *i.e.,* addition of acetoacetic and malonate esters.



3-Methyl-1, 5-
Hexane Dione

It is, however, pertinent to mention here that the **extra ester moiety** is invariably added to make it relatively easier to accomplish an *enolate-type construction* which may be cleaved as CO_2 as and when required.

Michael Reaction. It is mainly a base-promoted conjugate addition of *carbon nucleophiles* **(donors)** to *activated unsaturated systems* **(acceptors)** as given below :



2, 4-Pentane dione
[Donor]

1-Methylene
Acetone
[Acceptor]

*A. Michael, *J. Prakt. Chem.,* [2] **35**, 349 (1887).

J.d' Angelo *et al., Tetrahedron Asymmetry,* **3**, 459–505 (1992).

The various types of *donors, acceptors* and *bases* that are used in *Michael Reaction* are stated as under :

DONORS. Acetoacetates ; Aldehydes ; Carboxylic esters ; Cyanoacetates ; Ketones ; Malonates ; Nitriles ; Nitro compounds ; and Sulfones.

ACCEPTORS. Aldehydes ; Amides ; Carboxylic acids ; Esters ; Nitriles ; Nitro compounds ; Phosphonates ; Phosphoranes ; Sulphoxides ; Sulphones ; and α, β-Unsaturated ketones.

BASES. $H_3C.CH_2ONa$; $NH(CH_2CH_3)_2$; KOH ; KOC $(CH_3)_3$; $N(C_2H_5)_3$; NaH.

2.4. STREOCHEMISTRY

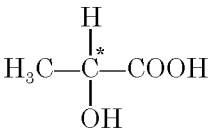
The fundamental basis of **'organic chemistry'** is predominantly dependent on the very relationship existing between the *molecular structure* and their corresponding *characteristic properties*. Therefore, the particular aspect of the science that exclusively deals with chemical structure *in three dimensions** (3D) is commonly known as **stereochemistry** (Greek : *stereos,* solid).

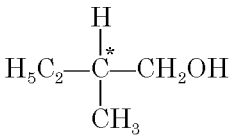
Isomers, are different compounds but they essentially have the identical molecular formula. Hence, in other words, the specific type of isomers that are apparently different from each other **only** in the manner the atoms are strategically oriented in space (but are more or less like one another with regard to which atoms are linked to which other atoms) are usually termed as **stereoisomers** ; and this phenomenon is known as **stereochemistry.**

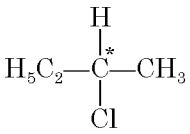
2.4.1 The Chiral Centre

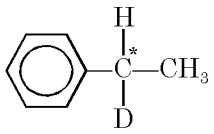
A carbon atom to which four different groups are attached is known as a **chiral centre.** [Quite often it is also termed as *chiral carbon*, so as to make a clear cut distinction from *chiral nitrogen, chiral phosphorus* etc.].

Examples


Lactic Acid


2-Methyl-1-butanol


sec-Butyl chloride


α-Deuterioethyl benzene

Salient Features. There are a few salient features of a **chiral centre**, namely :

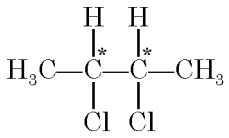
(*i*) Most–**but not all**—molecules that essentially have a *chiral centre* are chiral,

(*ii*) Most–**but not all**—chiral molecules contain a *chiral centre,*

(*iii*) *Exceptions.* There are certain molecules which contain chiral centres and yet they happen to be **achiral** *e.g.,*

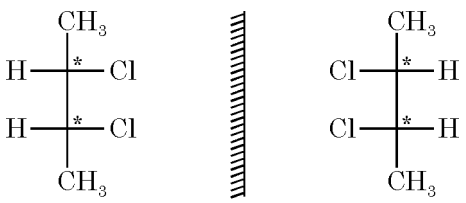
---

* 3D = A structure which has length, breadth and depth *i.e.,* it must lie in X- , Y- , and Z-axis.



meso-2, 3-Dichlorobutane

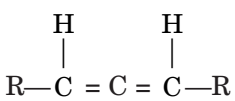
Explanation. *A* **meso compound** *is one whose molecules are superimposable on their corresponding mirror images even though they contain chiral centres.* Thus, *a meso* compound is **optically inactive** by virtue of the fact that the molecules are **achiral :** the rotation caused by one molecule is cancelled by an equal and opposite rotation afforded by another molecule which is the mirror image of the first, as shown below :



2, 3-Dichlorobutane
Mirror images superimposable
(A meso compound)

Note : Such achiral molecules invariably possess more than one chiral centre. In case, a molecule contains only one chiral centre, one may be pretty sure that the molecule is chiral.

(*iv*) Interestingly, there could be chiral molecules which may not contain any **chiral centre(s)** at all, such as :



A Substituted Allene

In short, one may be inclined to infer that the *presence* or *absence* of a *chiral centre* is, therefore, no criterion of chirality.

Generally, a **target-drug-molecule** with *n* chiral centres invariably has **2^n possible stereoisomers.** It is, however, pertinent to mention here that unless and until chiral reagents are used, **optically inactive starting materials** essentially give rise to **optically inactive** products, even though a **chiral centre** is formed.

It has been observed that a number of naturally occurring substances, such as : *an amino acid, a carbohydrate or a terpene* invariably contains **stereoisomers** which is skilfully exploited by the wisdom of a research chemist by using one stereoisomer as a starting material in plethora of modern synthesis. However, the following important *salient features* have to be taken into consideration :

(*a*) Chiral centre or centres inherently associated in the molecule afford certain extent of *'stereochemical control'* upon the view centres being generated,

(*b*) Proper utilization of reactions having predetermined *'stereospecificity'* is of utmost significance in such sequence(s), and

(*c*) By virtue of the *'kinetic control'* a research chemist may induct additional centres of chirality in a situation when one **diastereomer** is formed in a much more rapid manner than the other or by the aid of *'equilibrium control'* to produce the more stable isomer abundantly and conveniently.

In *stereochemistry*, the *three* types of control measures *viz.,* stereochemical, kinetic and equilibrium, the **first** one *i.e.,* **'stereochemical control'** is of prime value and significance in designing a new **'target-drug-molecule.** Therefore, the most prevalent and vital reactions that specifically afford **'stereochemical control'** are grouped together and summarized as stated under :

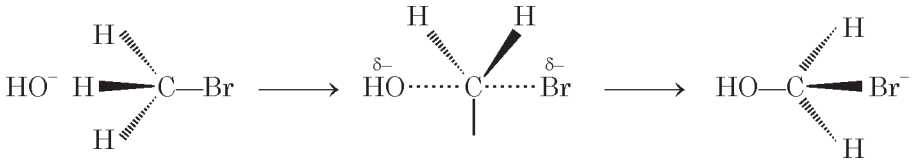
2.4.1.1 Nucleophilic Substitutions (S_N2) : Inversion of Configuration

The interaction between *methyl bromide* and *hydroxide ion* to produce *methanol* is a consequence of *second-order kinetics ; i.e.,* the rate of reaction is solely dependent upon the concentrations of both reactants as shown below :

$$\underset{\text{Methyl Bromide}}{CH_3Br} + OH^- \longrightarrow \underset{\text{Methanol}}{CH_3OH} + Br^-$$

$$\text{rate} = k[CH_3Br][OH^-]$$

The 'kinetics' of the above reaction is by virtue of the collision taking place between a CH_3Br molecule and OH^- ion. It has been proved beyond any reasonable doubt that the latter (OH^- ion) attacks the former (CH_3Br) from the rear side as illustrated below :



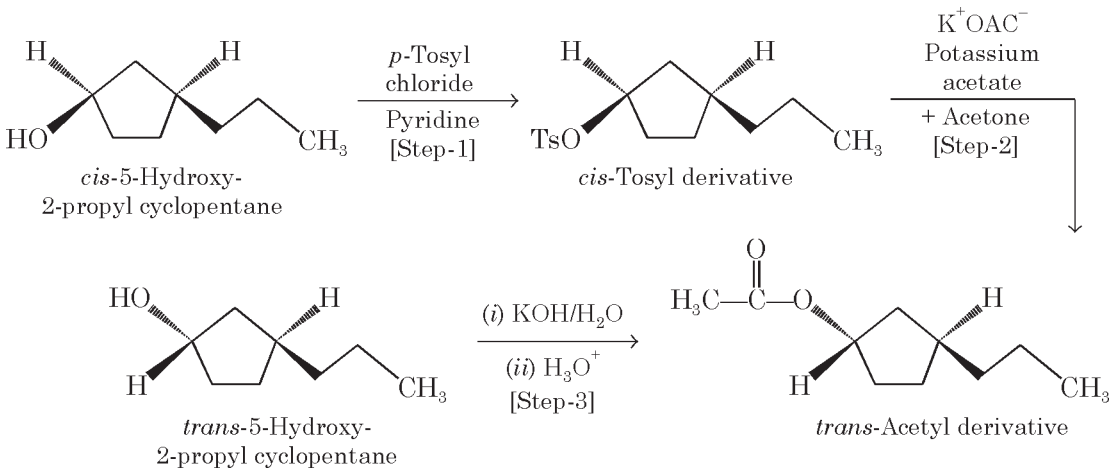
In the above reaction the OH^- ion strategically collides with a CH_3Br molecule farther away from the bromine, and when such a collision has sufficient energy, ultimately results into the formation of a *C—OH bond* and cleavage of a *C—Br bond*, thereby the **Br^- ion** is liberated free.

Thus, from the above reaction it is quite evident that the nucleophilic substitutions **(S_N2 reactions) proceed with the inversion of configuration.**

Example. Having gathered a clear concept about **'reaction selectivity'** one may accomplish the following *two* objectives by the help of nucleophilic substitutions (S_N2) :

(*a*) A chiral centre may be easily converted to one of the opposite configurations, and

(*b*) A *cis*-diastereomer may be changed into a *trans*-diastereomer.



The above cited example vividly shows the inversion of configuration of *cis*-5-hydroxy-2-propyl cyclopentane into *trans*—isomer *via* step-1 through step-3.

Explanation. The *three* steps involved in the above inversion of configuration may be explained as below :

Step-1. The *cis*-5-hydroxy-2-propyl cyclopentane on being treated with *p*-tosyl chloride (*i.e., p*-toluene sulphonyl chloride) in the presence of *dry pyridine* yields the corresponding *cis*-tosyl derivative.

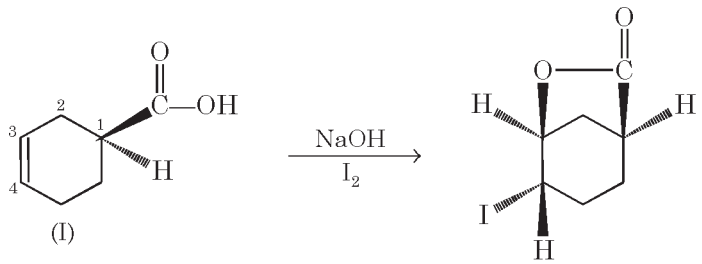
Step-2. The resulting *cis*-tosyl derivative undergoes acetylation at the free hydroxyl group with potassium acetate and acetone whereby an inversion of configuration takes place to give rise to *trans*-acetyl derivative.

Step-3. The *trans*-acetyl derivative is subjected to hydrolysis in an alkaline medium and subsequent treatment with a H_3O^+ gives the desired *trans*-5-hydroxy-2-propyl cyclopentane.

2.4.1.2 Ionic Additions to C—C Double Bonds. It has been observed that the ionic additions to C—C double bonds invariably proceed **stereospecifically** by means of *anti-addition* and **regiospecifically** following *Makovnikov orientation**. However, one must take into consideration the various **conformational factors** in the course of reactions involving **cyclic alkenes.**

Example. *Iodolactonization of cyclohexen-3-ene carboxylic acid (I).*

Interestingly, it is a typical example whereby an **intramolecular addition** to a **double bond** occurs within a **6-membered ring** as given below :



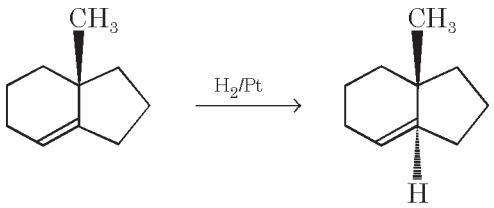
*__Markovnikov's Rule.__ In the addition of an acid to the C—C double bond of an *alkene*, the hydrogen of the acid attaches itself to the carbon that already holds the *greater number of hydrogens.*

Explanation. The HI liberated from $NaOH/I_2$ is added onto the prevailing double bond of cyclohexen-3-ene carboxylic acid (I), thereby affording an intramolecular addition, usually termed as *iodolactonization.*

2.4.1.3 Catalytic Hydrogenations

Generally, the catalytic hydrogenation are nothing but **syn**-*additions**. However, these reactions are able to be relied on as **stereospecific** in proceeding from the less-hindered side of the molecule. In instances, when the double bond is strategically located in a ring, the reaction involved is invariably **anti-***addition*** because it is *'anti'* to the main bulkiest substitutent.

Example. Catalytic hydrogenation of bicyclo [2, 1, 0] nona-1-en-6-methyl (I) to yield *bicyclo-nona-6-methyl* (II) as shown below :



(I) (II)

Explanation. When the catalytic hydrogenation of bicyclo [2, 1, 0] nona-1-en-6-methyl (I) is carried out, one of the H-atoms essentially adopts the **anti**-addition as shown in (II) above, as it is *'anti'* to the bulkiest substituting methyl group.

2.4.1.4 Acid-or Base-promoted Enolization of Compounds. In the case of acid- or base-promoted enolization of compounds *two* different types of **isomers** are usually accomplished, namely :

(*i*) **Stable Isomer(s).** The compounds wherein the *chiral centre* is located *alpha* to a *carbonyl* $\left(\begin{array}{c} O \\ \| \\ -C- \end{array}\right)$ *function* normally gives rise to a comparatively more stable isomer, and

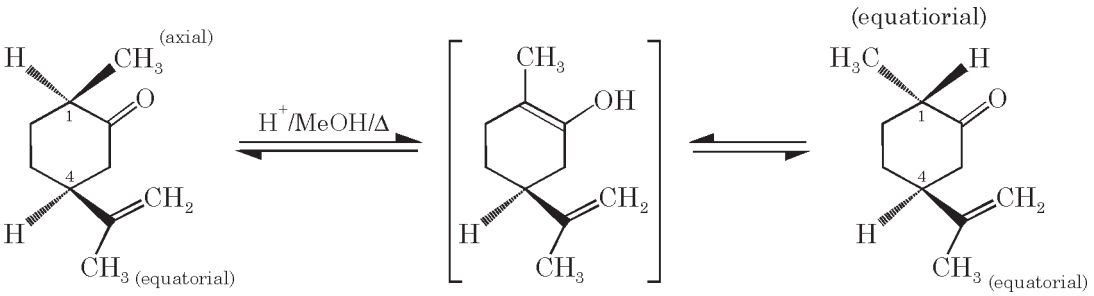
(*ii*) **Mixture of Isomers.** When the difference in *'free energy'* of the *two isomers* are not significantly wide apart one may end-up with a mixture of isomers.

Example. Conversion of *isodihydrocarvone*—a terpenoid derivative, into the corresponding *dihydrocarvone* analogue—a characteristic flavour in cloves, is accomplished by heating either with an *acid* or a *base* as illustrated below :

---

*__syn-__*addition.* It indicates stereochemical facts that the added groups become attached to the same faces **(syn)** of the double bond.

__anti-__*addition*. It indicates stereochemical facts that the added moieties get attached to the opposite faces **(anti) of the double bond.



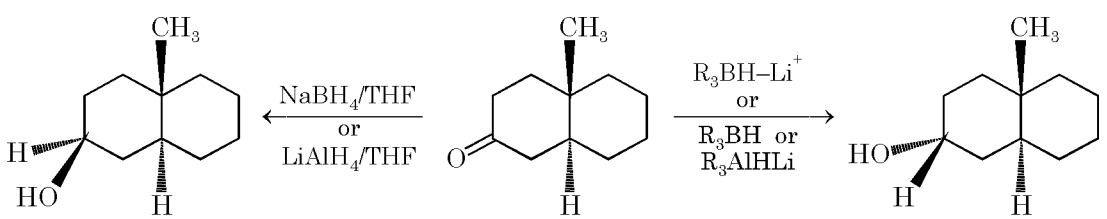
It may, however, be observed that the above two compounds are **diastereomers** *i.e.,* their stereoisomers are not mirror images of each other ; and **not enantiomers.*** Therefore, these compounds essentially have :

(*i*) Different values of *free energy,* and

(*ii*) *Specific optical rotations* that are neither equal nor oppositive.

In isodihydrocarvone, the orientations of hydrogen and methyl group at the apex of cyclohexane are **axial bonds,****, whereas those of hydrogen and methylene ethyl moiety at C-4 are **equatorial bonds.***** But in the converted dihydrocarvone the two attachments at C-1 and C-4 are **equatorial bonds.**

2.4.1.5 Reductions of Cyclohexanones. Stereoselective reductions based on complex borohydrides have proved to be of immense value in many instances ; in particular they have been of great practical application in the synthesis of epimeric cyclic alcohols. It has been observed that the reductions of cyclohexanones invariably give rise to the *more stable equatorial isomer* in the presence of $NaBH_4$or $LiAlH_4$. Interestingly, the *less stable axial isomer* is specifically favoured with certain hindered reducing reagents, such as : $R_3BH^-Li^+$, R_2BH, and R_3AlHLi, as shown below :



Equatorial alcohol (More stable) — A cyclohexanone — Axial alcohol (Less stable)

$NaBH_4$ = Sodium Borohydride ; $R_3BH - Li^+$ = Quaternary Lithium Borohydride ion ;

THF = Tetrahydrofuran ; R_3BH = Tertiary Borohydride ;

$LiAlH_4$ = Lithium aluminium hydride ; R_3AlHLi = Tertiary Lithium Aluminium Hydride.

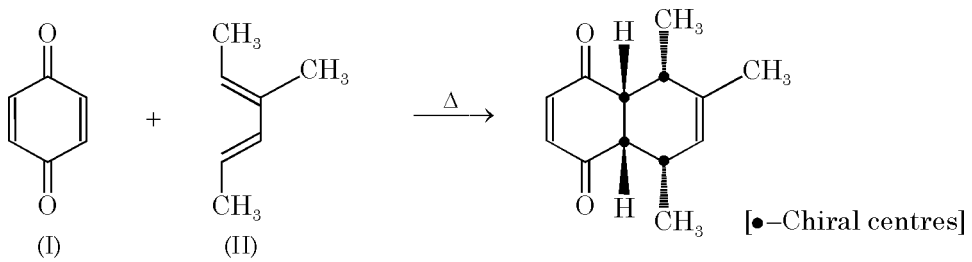
---

* **Enantiomers.** Mirror-image isomers are termed as **enantiomers.**

** **Axial Bonds.** The bonds holding the hydrogen atoms that are above and below the plane are pointed along an axis perpendicular to the plane are known as **axial bonds.**

*** **Equatorial Bonds.** The bonds holding the hydrogens that are in the plane of the ring lie in a belt about the **'equator'** of the ring are called **equitorial bonds.**

2.4.1.6 Cycloadditions. In fact, cycloadditions like the Diels-Alder reaction are *syn additions* wherein the maximum overlap of the interacting π bonds eventually further governs the stereochemistry. In Diels-Alder reaction the 1, 4-addition of the double bond of a dienophile I (*i.e.,* 2, 4-cyclo hexene-1, 4-dione) to a conjugated diene II to generate a 6-membered ring, such that up to **four new stereocenteres** (*i.e.,* **chiral centres)** may be created simultaneously at one go, as depicted below :



2.5. SUMMARY

In the light of the various important and genuine points raised and discussed in sections 1 through 4 of this chapter one may logically infer and draw a conclusion that unlike the *inorganic reactions* that are relatively more rapid and faster, the **organic reactions** are equally slower. In reality, the plethora of organic reactions both simpler and complex ones are mostly found to be sluggish, needs manipulation carefully, requires gentle persuation, governed by stringent experimental conditions, demands high-degree of purity of starting materials and reagents guided by thousands of tested and tried organic name reactions, and above all the personal skill, talent, wisdom and imagination of the **'research chemist'** to arrive at the **'target-drug-molecule'** *via* proven and scientifically reproducible routes of synthesis.

Based on the latest developments and advancements in the highly specialized and emerging fields of computer assisted drug design (CADD) a research chemist is enabled to focus and have a closer realistic approach to the **'target-drug-molecule'** obviously with greater accuracy and precision in comparison to the relatively older techniques comprised of hit-and-trial methods. Nowadays, with the help of readily available up-to-date facilities in any reasonably good research laboratory one may prune down drastically and logically non-productive, time-consuming, useless, and highly speculative-imaginative concepts and ideologies converted into very few, most selective, well conceived, theoretically viable and feasible routes of synthesis. Starting from *ab initio* to accomplish the **'target-drug-molecule'**, a *research chemist* may reach his goal in the shortest possible time thereby saving a lot of hard currency squandered unknowingly and unintentionally by adopting age-old, unusually slower traditional methods of synthesis.

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CHAPTER 3

Performing the Reactions

3.1. INTRODUCTION

It is indeed of paramount importance to be absolutely certain of the results of a particular experimental procedure. Therefore, it is quite necessary and equally pertinent to ensure its *reproducibility ;* and to accomplish this specific characteristic feature it is mandatory that one must observe the *appropriate precautions* with regard to the proper preparations *i.e.,* the actual syntheses of a host of medicinally active pharmaceutical substances otherwise referred to as **'drugs'** in the present text.

However, while **'performing the reactions'** to arrive at the final desired *medicinal compound* one has to take into consideration a large number of specific real experimental conditions, equipments, procedures with a common prevalent objective in mind which is to obtain the **'maximum yield'** together with the **'highest purity'** of the synthesized **'drug'.**

A number of such *salient features* required to achieve optimized yield of highly purified end-products are, namely :

(*a*) Organic reactions involving the usage of air-sensitive reagents ;—necessiates reaction to be performed under *inert* and *anhydrous conditions,*

(*b*) Organic reactions that are sensitive to the 'presence of water' ;—requires reaction to be carried out as in (*a*) above,

(*c*) To ensure the 'usage of necessary glassware, apparatus, reagents, and above all the documented experimental procedure,

(*d*) To work-up and a quick TLC-system to follow up the subsequent steps in a multi-step synthesis,

(*e*) To ensure that the 'chosen-system of synthesis' matches well with the starting material,

(*f*) Monitoring the progress of certain reactions by means of known screening/testing methods, such as : TLC, GC, HPLC etc.,

(*g*) To ensure completion of ensuring reactions at each step before proceeding to the next one by means of testing methods stated under (*f*) above,

(*h*) To follow specific laid-down specific and sophisticated reaction modes, purification, distillation, fractional distillation, steam-distillation by making use of particular type(s) of laboratory set-ups,

(*i*) To concentrate the '*solvent extracts*' to arrive at the precipitation/crystallization of the end-product in a pure form.

A few typical experimental apparatus or assemblies that are commonly used in the synthesis of **'Drugs'** are, namely :

1. Solvent stills (with continuous still collecting head)
2. Reactions performed an elevated temperatures
3. Large scale reactions and slow addition of reagents
4. Low temperature reactions
5. Reactions above room temperature using a condenser
6. Mechanical stirrers
7. Mechanical shakers
8. Sonication
9. Crystallization at low temperature
10. Distillation under reduced pressure
11. Small scale distillation
12. Performing the reaction
13. Photolysis.

The figures (1) through (18) in this section have been adapted from *'Advanced Practical Organic Chemistry'*, Blackie Academic and Professional, London.

I. Solvent Stills

The most common and classical distillation set-up usually comprise of a distillation vessel, still-head, thermometer, double-surfaced condenser, receiver-adapter, and a collection vessel.

However, the synthesis of *'Medicinal Compounds'* usually makes use of a **'continuous still set-up'** which is essentially comprised of a distillation vessel, collecting head, and a condenser as shown in Fig. 3.1.

As evident from Fig. 3.1, continuous still systems essentially comprise of an **upright arrangement** which obviously takes up much less space as compared to the conventional-horizontal still set-up ; and a **'solvent-collector'** (collecting vessel) that is positioned strategically between the still-pot and the condenser.

Advantages :

(*a*) The continuous still set-up is designed in such a manner that the *'distilling solvent'* gets condensed and collected in a collecting head,

(*b*) Whenever, the collecting head is full the solvent simply goes back into the still pot through an overflow, thereby allowing distillation to take place continuously without any remote possibility of the still boiling absolutely dry, and

(*c*) Solvent may be drawn off from the collecting head as and when required ; and also poured back right into the still pot if not needed.

Note : In any case, it is NOT RECOMMENDED that any type of **'still-solvent'** is left on unattended for an indefinite prolonged periods of time.

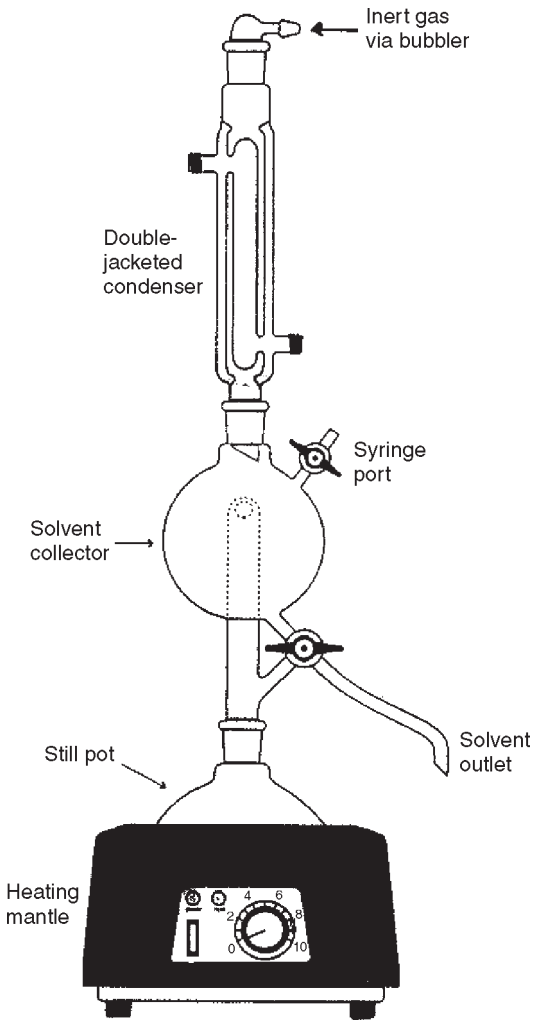

Fig. 3.1. Continuous still set-up.

In Fig. 3.2, a typical design for the continuous still collecting head has been illustrated. It is constructed from a round-bottom flask (2L-capacity), ground-glass cone, a 2-way tap, and a 3-way tap. The 2-way tap conveys the solvent to be withdrawn *via* a syringe, and is specifically suitable as well as convenient for **anhydrous solvents** only. On the other hand, the 3-way tap permits the solvent to be *collected, drawn off,* or *subsequently returned into the distillation pot simply with the flick of the tap.*

Note : 1. Size of the still pot depends upon the actual quantity of solvent required. Usually, a maximum of 5L capacity still is more than sufficient under any prevailing *'laboratory conditions' vis-a-vis* requirements.

2. Still head must always be **smaller** in its capacity in comparison to the still pot in order to avoid the possibility of the **still pot boiling dry.**

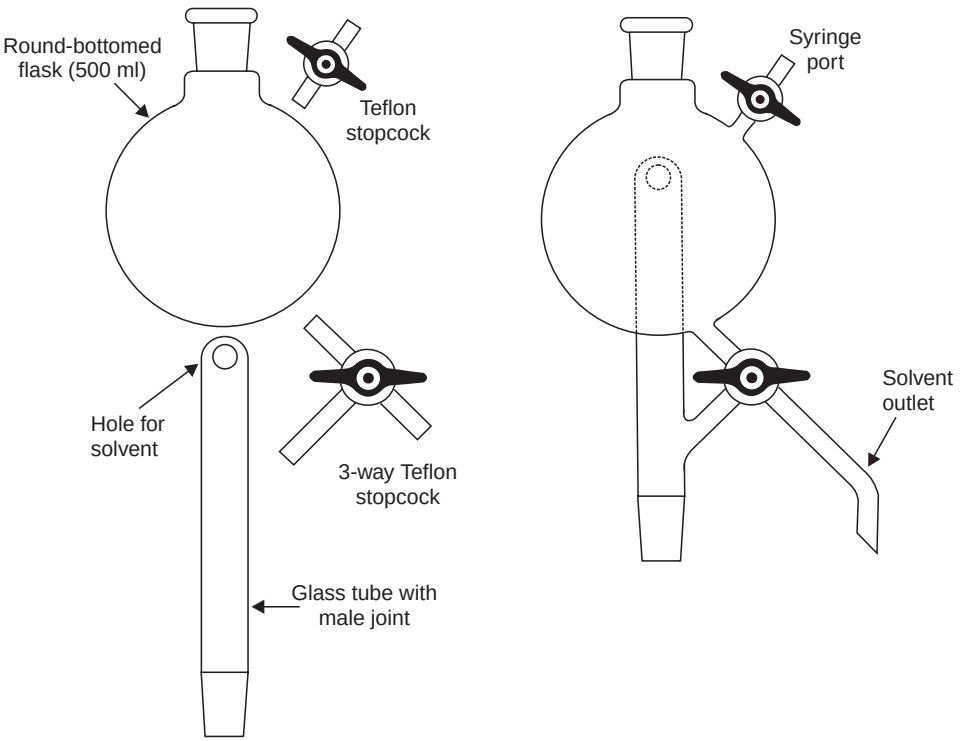

Fig. 3.2. Continuous still collecting head.

Cautions. The following precautionary measures are a must in setting up a **'continuous still'**, namely :

1. A double-walled water condenser should be fitted especially for the lower-boiling organic solvents.
2. All ground glass joints must be fitted with **Teflon sleeves** so as to afford a perfect seal, and also to avoid frequent jamming. Likewise, **Teflon taps** should always be preferred in place of glass taps in the collecting head specifically.
3. Never to **USE GREASE** on the glass joints because it will be definitely leached out by the hot-solvent ; thereby not only contaminating the *'solvent'* but also causing the joints to stick.
4. *For Anhydrous Solvents.* The continuous still system must be provided with an **'inert atmosphere'** by connecting it to a *nitrogen* or *argon* line (Fig. 3.1).

Note : It is always advisable and most important to make use of either **OIL BUBBLERS** or similar devices so as to avoid the usual suck back when the still is getting cooled to room temperature (*i.e.,* when it is NOT IN USE). It may also be *'remedied'* by turning up the flow rate of the **'inert gas'** during such period when the still is getting cooled. The *'oil bubbler'* also helps in the release of increased gas volume in the still, if any, to avoid any possible explosion.

II. Reactions Performed at Elevated Temperatures

In a situation, when a reaction is required to be heated or there exists a possibility that it might be **'exothermic'** in nature, it is absolutely necessary to incorporate a *condenser* into the reaction assembly, as depicted in Fig. 3.3.

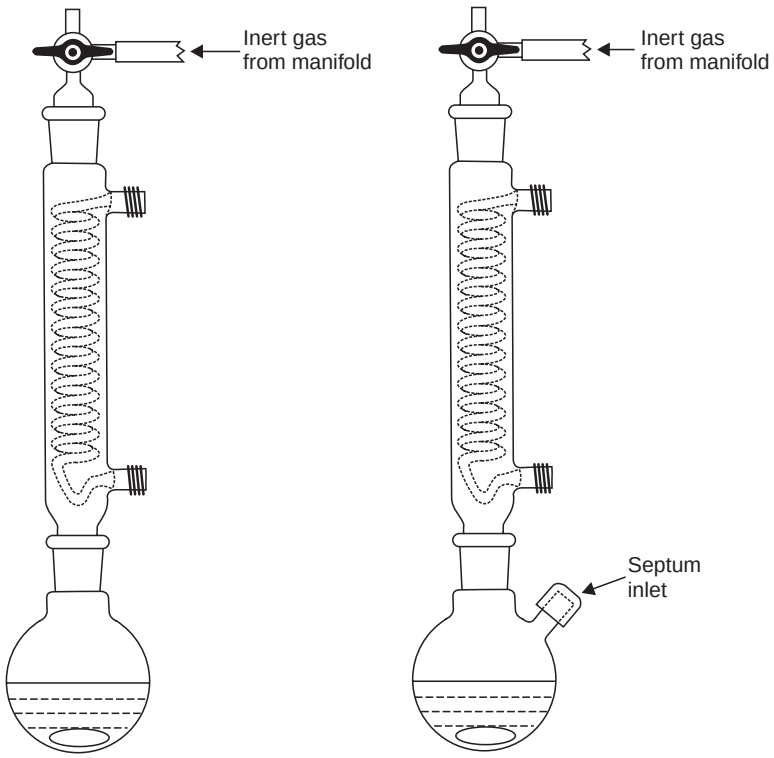

Fig. 3.3. Reaction set-up with a condenser (For Exothermic Reactions).

In fact, Fig. 3.3, illustrates the typical set-ups exclusively meant for carrying out such reactions which are required to be heated either for a shorter or longer duration.

Salient Features. The various salient features for reaction set-up with a condenser are as enumerated below :

1. It is always a better method to use **'coil-type condensers'** especially for carrying out reactions under absolutely **'INERT CONDITIONS'.**
2. Ordinary *Liebig condensers* do have the water-jacket next to the outer-surface ; and therefore, there exists an enhanced chances and possibility of atmospheric moisture getting condensed on its outer-surface, running down to the ground glass joint, and ultimately seeping into the reaction flask slowly and steadily. However, this serious problem of contamination may be negated by using *Teflon sleeved joints* almost completely.

In actual practice, it is invariably required to add reagent(s) into the reaction flask while the reaction is still going on ; and this can be accomplished easily by making use of a flask with a *side-arm fitted with a 'septum-inlet'* (Fig. 3.3).

Note : It is equally important to observe while the temperature of an on-going reaction is undergoing a change progressively the bubbler of the system must be checked thoroughly to ensure there exists a CONSTANT INERT GAS PRESSURE in the prevailing system.

III. Large Scale Reactions and Slow Addition of Reagents

In a plethora of syntheses in 'pharmaceutical substances' it is invariably required for the slow and gradual addition of an **'air-sensitive reagent'** right into the on-going reaction in the reaction flask itself. Hence, it may be accomplished in a best possible manner by incorporating a **'pressure equalizing addition funnel'** into the apparatus. Importantly, for large scale reactions this is always the best choice assemly in a chemical laboratory.

Fig. 3.4 evidently depicts the assembly for performing large-scale reactions, in an inert atmosphere as well, and with a convenient provision for the slow addition of reagents.

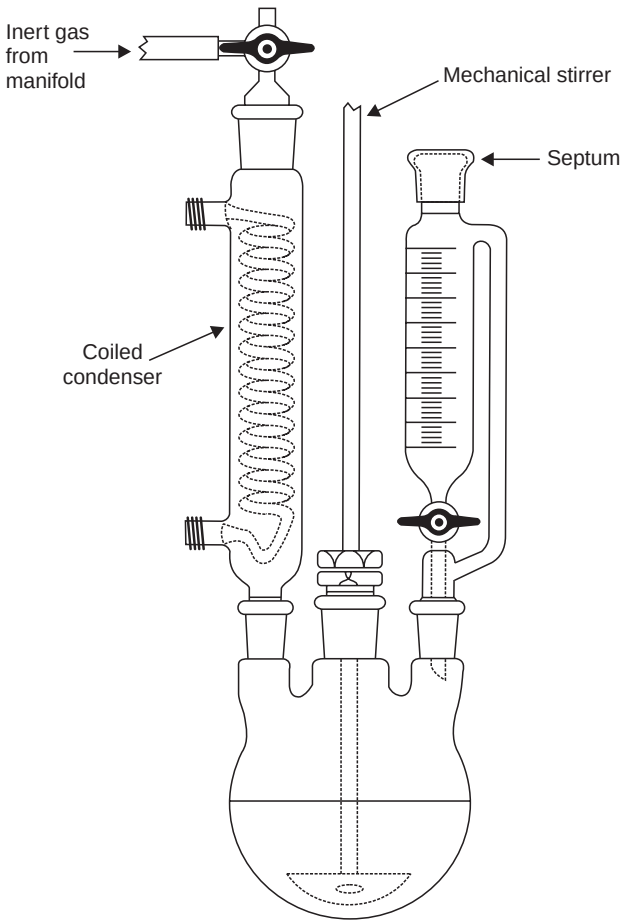

Fig. 3.4. Reaction set-up with a provision for slow addition of reagents and large scale reactions.

IV. Low Temperature Reactions

In general, reactions are performed below room temperature by simply placing the *'reaction vessel'* in a cooling bath. It may, however, be accomplished by placing an appropriate cooling

mixture into a lagged bath ; and subsequently allowing the reaction vessel to be *'immersed'* in the cooling mixture to a certain depth thereby making sure that the *'reaction contents'* are actually much below the level of coolant. However, the temperature of the coolant may be monitored periodically by the help of a *low-temperature thermometer* duly immersed in the bath. A typical low temperature reaction assembly very commonly employed in a chemical laboratory is shown in Fig. 3.5.

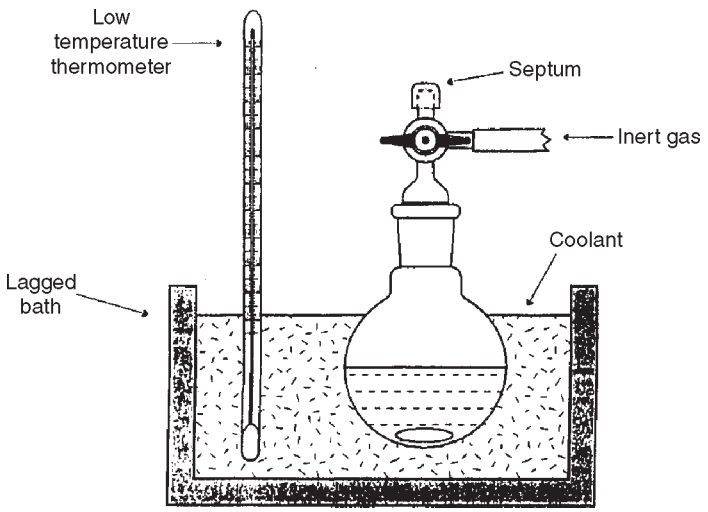

Fig. 3.5. A simple reaction set-up for performing reactions at low temperature both with or without an inert gas environment.

It is pertinent to mention here that invariably when carrying out reactions employing cooling baths, that the temperature of the reaction mixture may not be at the same temperature as that of the bath due to *'exothermic processes'* occurring ; and, therefore, it is absolutely necessary, wherever feasible, to monitor the prevailing **'internal-reaction temperature'.** An easy and convenient way to accomplish this is to use a **digital low-temperature thermometer** duly positioned in the reaction vessel as shown in Fig. 3.6, wherein a **'hypodermic probe'** that may be inserted right into the reaction flask through a strategically positioned *'septum'.*

Broadly speaking most low temperature reactions must be performed under an inert atmosphere of either *Nitrogen* or *Argon dry gas* in order to avoid the possibility of **'atmospheric moisture'** beng inadvertently condensed into the reaction mixture.

In fact, there are **THREE** frequently and abundantly variants of cooling mixtures that are used in a *'chemical laboratory'* , namely :

(*a*) Ice-Salt Baths,

(*b*) Dry Ice-Solvent Baths, and

(*c*) Liquid Nitrogen Slush Baths.

These different types of 'baths' shall now be discussed briefly as under :

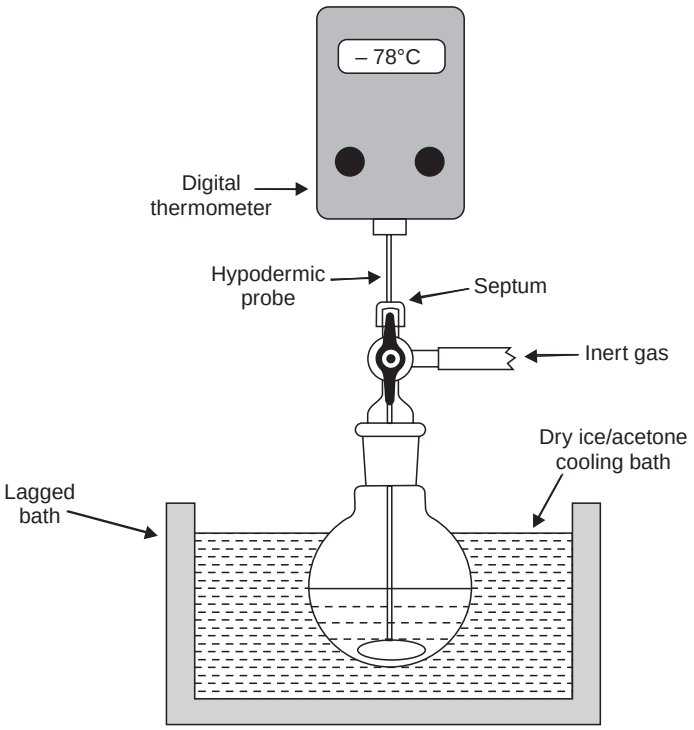

Fig. 3.6. A low temperature reaction assembly using a digital-low temperature thermometer and a 'hypodermic probe'.

1. Ice-Salt Baths

A variety of inorganic salts and solvents may be mixed in appropriate ratios along with crushed ice to give rise to **sub-zero temperatures.** In actual practice, however, one may accomplish lower temperature ranges varying between 0°C to – 40°C as depicted in Table : 1 below :

Table 1. Ice Based Cooling Baths*

Additive	*Ratio [Ice : Additive]*	*Temperature (°C)*
Water	1 : 1	0
Sodium Chloride	3 : 1	– 8
Acetone	1 : 1	– 10
Calcium Chloride (Hexahydrate)	4 : 5	– 40

Note : It is worthwhile to observe here that at the lower temperatures the cooling mixtures mostly comprises of fine granular ice-salt particles having either a little or no liquid, which may ultimately give rise to *poor thermal contact* with any reaction vessel immersed in it.

*Gorden, A.J., and Ford R.A., **'The Chemists Companion',** J. Wiley & Sons, New York, 1972.

Therefore, it is always preferable to make use either of a **'liquid cooling'** or **'slush coolant'**, for affecting careful and rigid control at lower temperature by virtue of the fact that both of them afford good thermal contact with any reaction vessel immersed in it.

2. Dry Ice-Solvent Baths

In fact, solid CO_2 is known as *'dry-ice'* commercially which is frequently available either as pellets or blocks. It really gives rise to very effective and good *'cooling mixtures'* when mixed with appropriate organic solvents to obtain temperatures ranging from – 15°C to – 78°C as depicted in Table 2 under :

Table 2. Dry-Ice Cold Baths Using Organic Solvents*

Organic Solvent	*Temperature (°C)*	*Organic Solvent*	*Temperature (°C)*
Ethylene glycol	– 15	Chloroform	– 61
Carbon tetrachloride	– 25	Ethanol	– 72
Heptan-3-one	– 38	Acetone	– 78
Acetonitrile	– 42		

3. Liquid Nitrogen Slush Baths

Slush baths are usually made by adding **'liquid nitrogen very carefully'** to a *specific organic solvent* previously contained in the bath, with constant stirring with a glass rod or some convenient mechanical device (*e.g.,* stirrer). Interestingly, the coolant must attain the consistency of ice-cream, and stirring would certainly prevent any possible solidification. Evidently, a wide range of organic solvents will give rise to a broad spectrum of low temperatures ranging from + 13°C to – 196°C, as given in Table 3.

Importantly, such cooling systems may be used efficiently for several hours at a stretch if the cooling-bath is adequately lagged (*i.e.,* insulated). Besides, in such situations that demand a prolonged-cooling (say-overnight) then the reaction-vessel may either be kept in a refrigerator itself or cooled by the use of a **'portable commercial refrigeration unit'.**

Table 3. Liquid-N_2 Slush Baths Using Organic Solvents**

Organic Solvent	*Temperature (°C)*	*Organic Solvent*	*Temperature (°C)*
para-Xylene	13	Chloroform	– 63
para-Dioxane	12	Isopropyl acetate	– 73
Cyclohexane	6	Butyl acetate	– 77
Formamide	2	Ethyl acetate	– 84
Aniline	– 6	2-Butanone	– 86

*Philips A.M., and Hume J., *J. Chem. Ed., 54*, 664 (1968).

**Rondeau R.E., *J. Chem. Engg. Data, 11,* 124 (1966).

Diethylene glycol	– 10	Isopropanol	– 89
Cycloheptane	– 12	*n*-Propyl acetate	– 92
Benzyl alcohol	– 15	Hexane	– 94
ortho-Dichlorobenzene	– 18	Toluene	– 95
Carbon tetrachloride	– 23	Methanol	– 98
ortho-Xylene	– 29	Cyclohexane	– 104
meta-Toluidine	– 32	Isoctane	– 107
Thiophene	– 38	Carbon disulphide	– 110
Acetonitrile	– 41	Ethanol	– 116
Chlorobenzene	– 45	Methyl cyclohexane	– 126
meta-Xylene	– 47	*n*-Pentane	– 131
Benzyl acetate	– 52	Isopentane	– 160
n-Octane	– 56	Liquid Nitrogen	– 196

V. Reactions Above Room Temperature Using A Condenser

Invariably, for reactions at an elevated temperature or above room temperature it is very important and absolutely necessary to use an **'open-system'** that does *not* ultimately lead to a *build-up of pressure* inside the reaction vessel.

Fig. 3.7 represents the diagrammatic sketch of a reaction vessel protected with a condenser. In fact, the condenser usually prevents the evaporation of volatile components (*i.e.,* the solvent) from the on-going reaction mixture.

A good number of altogether different designs (shapes) of condenser are available that are meant to be used for a specific purpose and also the nature of reaction involved. These condensers are of **FOUR** different types, namely :

(*a*) **Liebig Condenser** [Fig. 3.8(*a*)]. In this condenser, the water *flows in* at the **bottom** and **flows out** at the **top** thereby providing a jacket full of cold water all around the condenser stem, and ultimately leading to a cold surface on the inside. Thus, any volatile components present in the reaction mixture get condensed on the cold outer surface and run back right into the reaction mixture instantly.

(*b*) **Coil Condenser** [Fig. 3.8(*b*)]. The coil condenser almost functions in an identical fashion except that the *'cold surface'* is now located on the inner side of the condenser.

Advantage. It has an edge over the Liebig condenser since it can specifically used in *humid locations,* as there exists much less possibility as well as tendency for the atmospheric moisture to get condensed on the outside of the condenser and subsequently, run down over the prevailing reaction vessel.

(*c*) **Double-Jacketed Coil Condenser** [Fig. 3.8(*c*)]. It is also water-cooled ; and water *flows in* at the **bottom** and *flows out* at the **top.** The **specific design** of double-jacketed coil condenser tends to be more efficacious and versatile than both Liebig's and coil condensers by virtue of the fact that it caters for a definite greater area of cold surface.

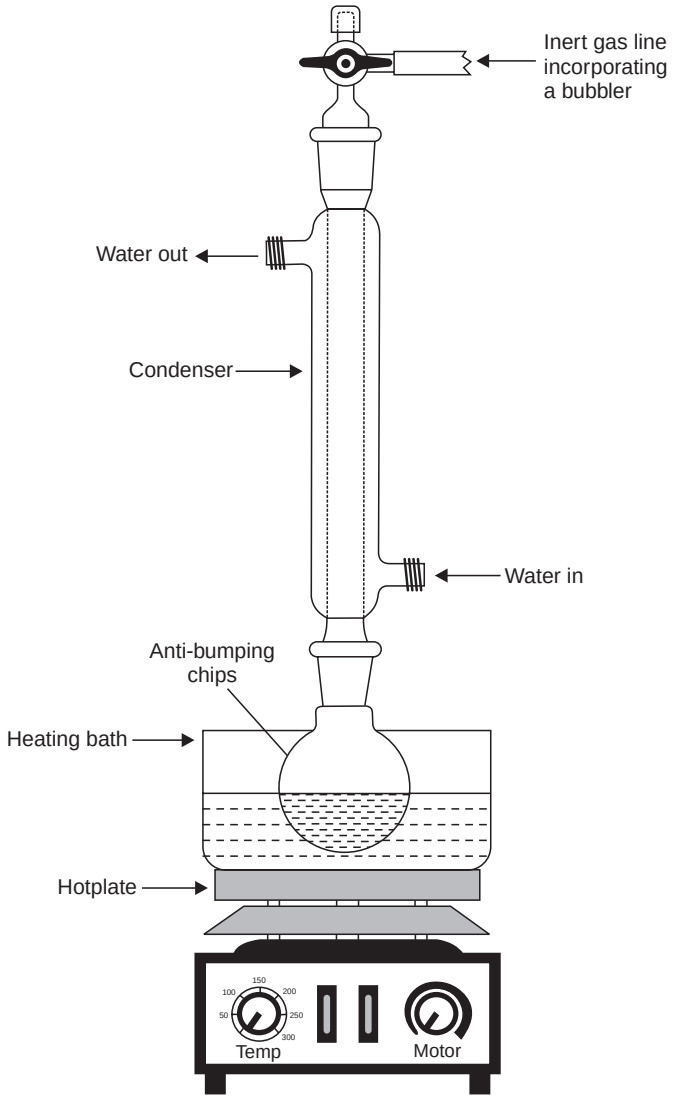

Fig. 3.7. A reaction vessel protected with a condenser

Advantage. It is always preferred when dealing with low-boiling organic solvents (having bp ≤ 40°C) *e.g.,* solvent, ether.

(*d*) **Cold-Finger Condenser** [Fig. 3.8(*d*)]. In this specific case the coolant is strategically placed in the **top** of the condenser, and more coolant could be added as and when required. Thus, this gives rise to an **extremely cold surface** on the *inside of the condenser.*

Advantages. These type of condensers are invariably used for such reactions that exclusively involve solvents or components that either boil at or below the room temperature, such as : liquid ammonia (bp – 33°C). Besides, they may also be employed for host of other higher boiling range solvents as well.

Fig. 3.8 evidently illustrates all the aforesaid *four* different types of condensers (*a*) through (*d*) respectively.

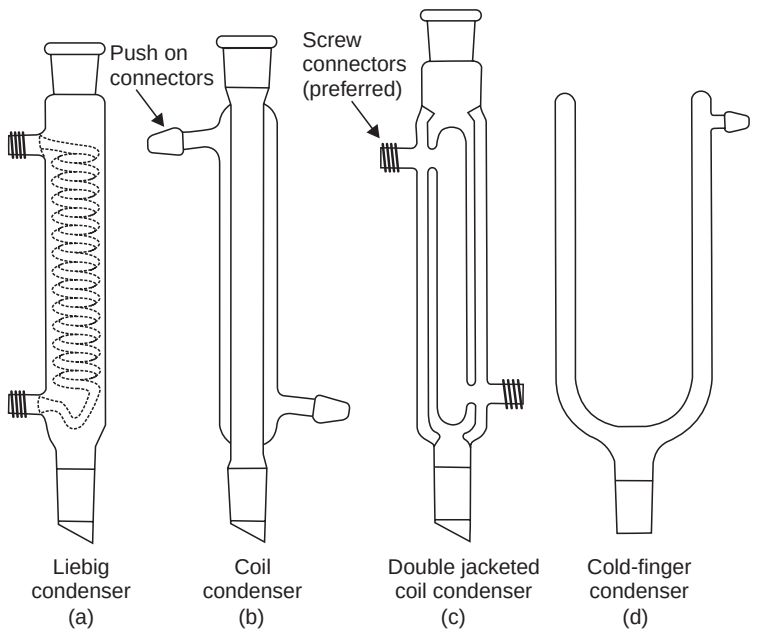

Fig. 3.8. Four types of condensers.

VI. Mechanical Stirrers

Mostly the mechanical stirring machines (devices) essentially comprise of a variable-speed electric motor adequately clamped and strategically positioned just above the reaction vessel, which causes stirring due to a rotating vertical rod (normally glass, but can also be made up of stainless-steel or Teflon). Usually a paddle or vane (*i.e.,* the blade of a propellar) is attached to the bottom end of this rod. The rotating action of the rod with the vane or paddle is solely responsible for agitation of the reaction mixture as shown in Fig. 3.9.

Salient Features. The various salient features of a mechanical stirring assembly are as given below :

1. Both rod and vane are normally detachable so as to enable different length rods and different sized paddles may be employed as per the appropriate need and requirement.
2. Speed of the stirrer can always be adjusted by the help of a variable-speed device on the motor.
3. Various shapes and designs of vanes are available, the most frequently used being a crescent-shaped piece of TEFLON about 5 mm thick. It has a specific slot in it which permits it to be detached easily from the glass rod, as can be seen from Fig. 3.10. In this particular design the vane may be rotated about a *horizontal axis.* Therefore, it can be easily and conveniently inserted through the narrow neck of a round-bottomed flask, and subsequently, rotated into a horizontal position ready for use.

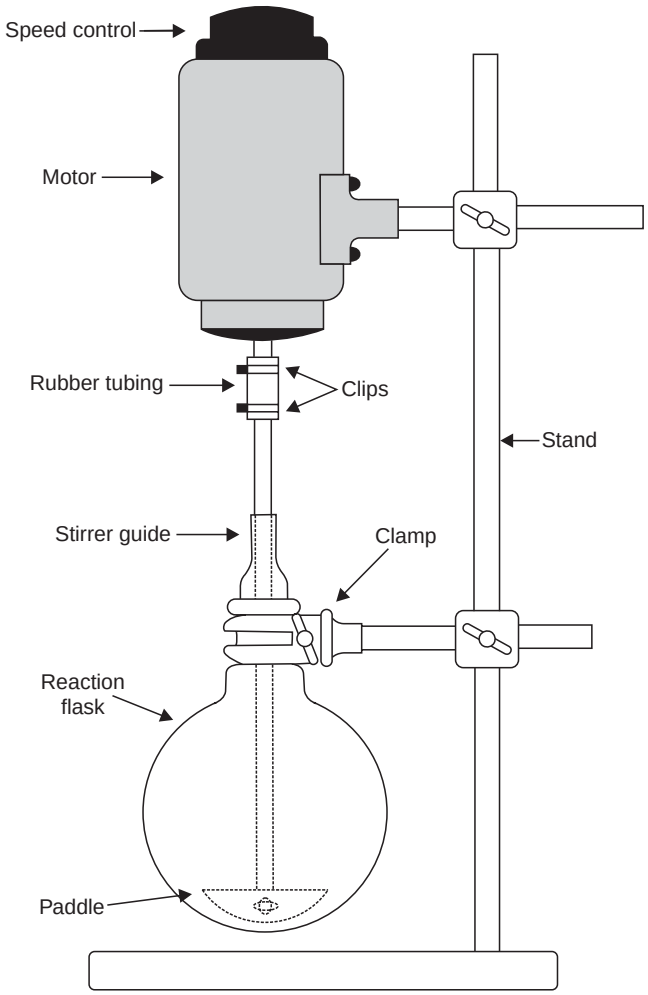

Fig. 3.9. Mechanical stirring machine with variable-speed electric motor.

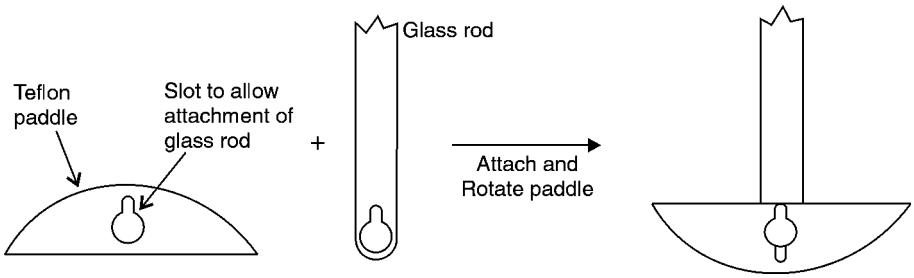

Fig. 3.10. A crescent-shaped vane made of Teflon about 5 mm thick.

VII. Mechanical Shakers

It is more or less a simple mechanical device equipped with motors having variable-speed which will shake an attached reaction flask, as shown in Fig. 3.11 on next page. Here, the

flask, is clamped securedly to the shaker, and must be provided with a counter-balance flask so as to maintain the balance of the machine.

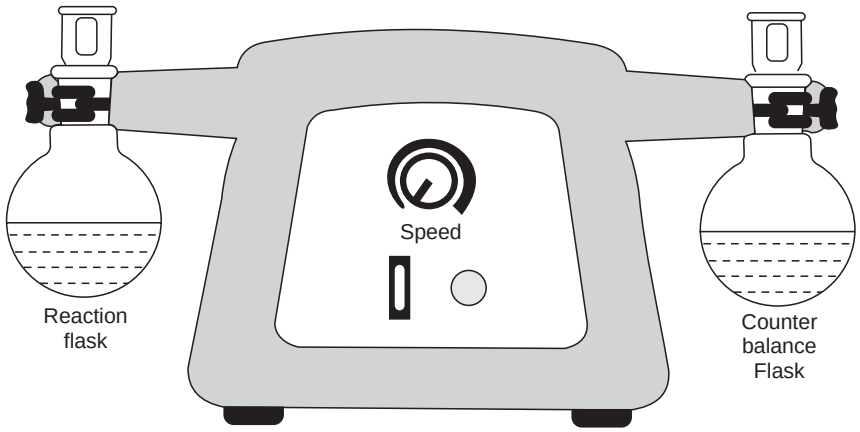

Fig. 3.11. A simple mechanical shaker with a variable-speed device.

VIII. Sonication

With the advent of recent technological advancement the **'ultrasonic waves'** may be exploited as a means of agitation, otherwise known as *sonication*. The most commonly used assembly makes application of a simple ultrasonic bath, in which the reaction vessel is positioned as illustrated in Fig. 3.12.

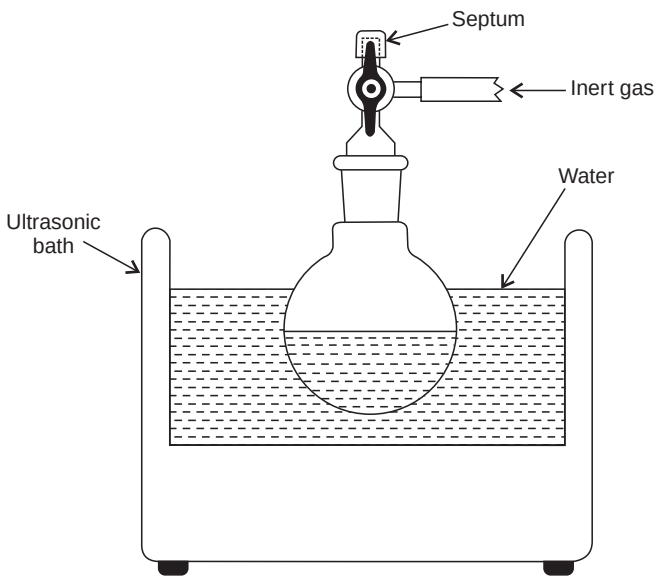

Fig. 3.12. A simple ultrasonic bath.

Alternatively, **ultrasonic probes** may also be employed and are invariably arranged well inside the reaction vessel itself, as depicted in Fig. 3.13. This specific reaction assembly is particularly suitable as well as desirable under **two** arising situations, namely :

(*a*) In case, precise control of the ultrasound frequency is desired for the reaction, and

(*b*) In case, external control of the reaction temperature is an absolute necessity.

It is, however, pertinent to mention here that in either of the two situations (*a*) and (*b*) above, the ultrasonic waves are normally produced inside the reaction vessel whereby agitation of its contents can be caused effectively and progressively.

Nevertheless, the *sonication* is specifically beneficial for such reactions that essentially involve insoluble solids. In such a situation the ultrasonic waves help to break up the solid lumps/pieces into corresponding very small particles that ultimately facilitate tremendously the solvolysis phenomenon and hence the reaction process.

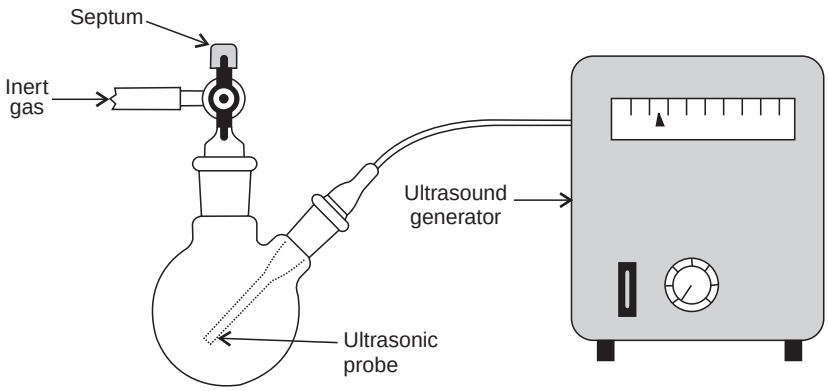

Fig. 3.13. An ultrasonic bath using ultrasonic probes.

IX. Crystallization at Low Temperature

An assembly for carrying out the crystallization at low temperature, for handling substances from medium to large scale, is shown in Fig. 3.14.

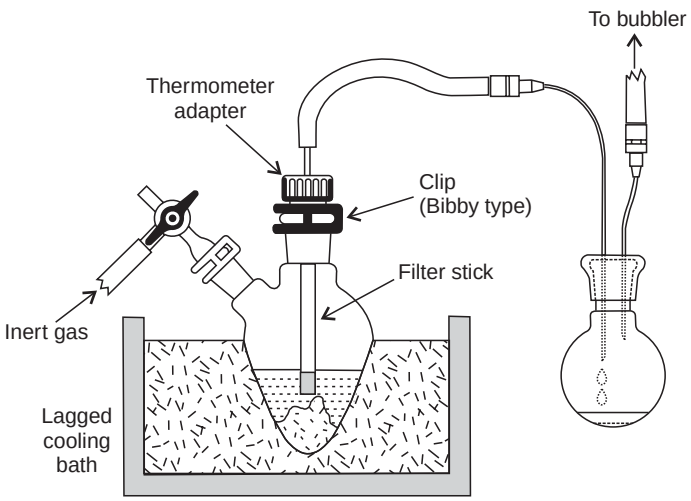

Fig. 3.14. Apparatus for crystallization at low temperature.

The impure product is made to dissolve in the minimum quantum of solvent at room temperature and is filtered into a two-necked pear shaped flask. Now, the flask is fitted with an inert-gas inlet and a thermometer-adapter having a filter-stick, connected to a bubbler. The filter-stick is held above the solution and the contents of the flask is purged with the 'inert-gas' and subsequently placed in a cooling bath. The cooling bath may be cooled gradually by slow addition of the cooling agent into the solvent. On completion of crystallization the bubbler is disconnected and the filter stick is subsequently connected to a suitable receiver with the help of a Teflon tubing (which is chemically inert). The filter-stick is now dipped into the solution and the mother-liquor is eventually forced through into the receiver by employing inert gas pressure. The resulting crystals may be washed by first releasing the inert-gas pressure, and subsequently adding small quantity of **precooled solvent** *via.* the 3-way tap, using a canula. The washings may be removed using the filter-stick as described earlier. The isolated crystals can be collected and dried in the usual manner.

X. Distillation Under Reduced Pressure

A plethora of organic compounds, their intermediates and above all the *'pharmaceutical substances'* are appreciably sensitive to undue thermal exposure ; and hence, may undergo *decomposition* when heated to their boiling points. Therefore, such compound(s) cannot be distilled at the atmospheric pressure. In such a situation it is always advisable and preferable to perform the distillation at a reduced pressure or under vacuo so as to avoid any possible thermal decomposition. However, the extent of reduction in the '*boiling point'* shall entirely depend on the *'extent of reduction in pressure'* ; and it may be estimated from a pressure-temperature monograph.

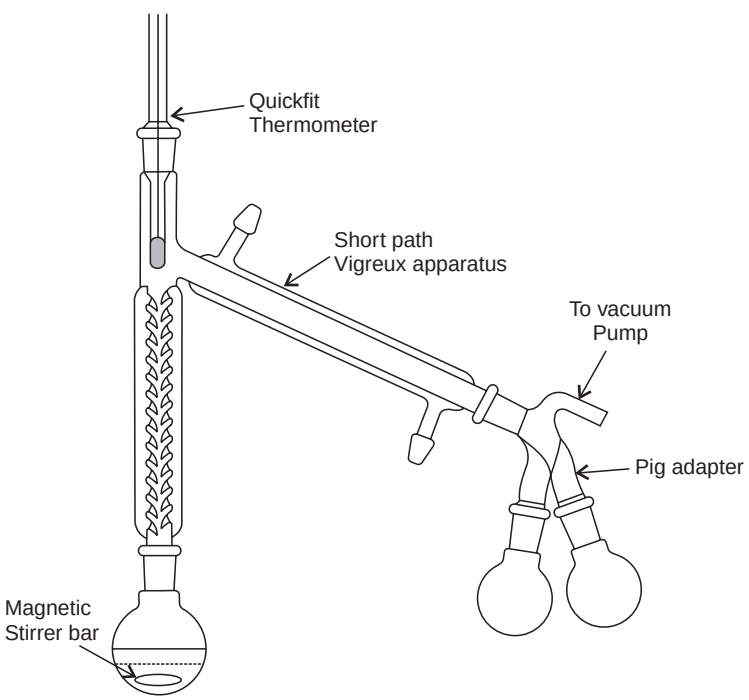

Fig. 3.15. Assembly for distillation under reduced pressure

A typical vacuum distillation apparatus is given in Fig. 3.15. The prominent and major difference in comparison to a simple distillation apparatus is in the design of the receiver adapter. The skilful design of the receiving adapter permits the collection of several fractions successively without breaking the initially attained vacuum in the distillation assembly.

Procedure. The various steps involved in performing a distillation under *reduced pressure* are as stated below :

1. Transfer the sample in the distillation flask **only upto 2/3rd full** and introduce a stirring bar or magnetic guide.

Caution :

(*a*) The use of *'anti-bumping granules'* should be avoided as these are not so effective under vacuo (*i.e.,* reduced pressure).

(*b*) Alternatively, a very narrow capillary that permits the in-flow of a gentle stream of air or nitrogen (analytical grade) bubbles to pass through the solution is found to be equally effective ; however, a brisk stirring employing a **magnetic follower** (or *magnetic guide* or *stirring bar*), in fact, is much more useful and convenient.

2. All apparatus in use must be thoroughly cleaned and oven dried. Before commencing the assembly of the apparatus a small quantum of **high vacuum grease** must be applied on the outer edge of each joint. Special care must be taken that the receiver adapter and the collection flasks are well secured using clips, and ultimately connect the assembly to preferably a double-stage **vacuum-pump** (heavy duty) with an appropriate trap between the pump and the assembly.
3. The liquid is stirred rapidly and open the apparatus to the vacuum with **utmost care.** At this stage certain amount of *bumping* and *frothing* may take place because of the ensuing evacuation of *air* as well as *volatile components.* In case, it is a dire necessity **one** may adjust the pressure to the desired value by permitting the inlet of inert gas into the system through a needle valve.
4. The flask must be heated slowly at the initial stage to drive off any volatile impurities, and subsequently to go ahead with the process of distillation. The **still-head temperature** must be *controlled and monitored carefully ;* and *a forerun* and *a main desired fraction* should be collected that must get distilled at a fairly constant temperature.

   Note. In case fractionation is the objective, one may have to meticulously collect a number of fractions ; and for this it is absolutely essential to allow the **'mixture'** to **undergo distillation very slowly and steadily.**
5. The distillation process, must be stalled (*i.e.,* stopped) as soon as the *'level of liquid'* in the flask is running low which may be accomplished by removing the heating-bath.
6. The apparatus is subsequently **'isolated'** from the vacuum and filled carefully with the **'inert gas'.** The flask(s) having the distillate shall remain under a dry and inert atmosphere and must be removed swiftly and adequately fitted with an air-tight septum to ensure the purity.
7. The vacuum pump, heating mantle should be switched off, and the cold-trap must be cleaned thoroughly before cleaning.

XI. Small Scale Distillation

In actual practice, the only predominant draw-back invariably encountered particularly with *small scale distillations* is that an appreciable quantum of the **'sample'** may be lost in *'wetting'* the surface of the column as well as the condenser. However, this crucial problem may be minimized substantially by making use of **very compact one-piece short-path designs**, but it does so at the cost of significantly reduced fractionating efficiency of the columns engaged, ultimately leading to much less effective separation.

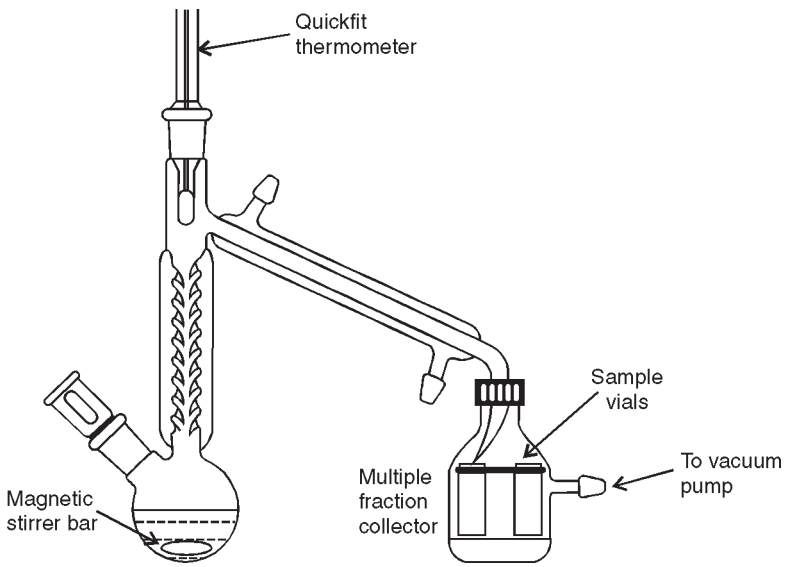

Fig. 3.16. Assembly for small scale distillation.

A most commonly used typical assembly designed for 'small scale distillation' essentially consists of a short Vigreux column* and a rotary fraction collector, as shown in Fig. 3.16.

XII. Performing the Reaction

Broadly speaking, reactions on relatively larger scales are usually performed in any good well equipped *'chemical laboratory'* after one has adequately established the requisite experimental parameters on a smaller scale.

In actual practice one comes across two entirely different situations, such as : (*a*) where the reaction on larger scale needs to be carried out at specifically low temperatures ; and (*b*) where the reaction on larger scale requires to be refluxed either for a shorter or longer duration.

Fig. 3.17 represents a diagramatic sketch of a rather simple and common laboratory set-up frequently encounterd particularly for low-temperature reactions carried out on larger scales. In case, the solution which is to be added from the dropping funnel essentially needs cooling prior to its addition into the reaction flask, it may be quite convenient and possible to engage a *jacketed dropping funnel,* having the cooling mixture (*e.g.,* dry-ice and acetone mixture giving about – 10°C) strategically placed in the jacket (see Fig. 3.17).

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*__Vigreux column.__ A short fractionating column.

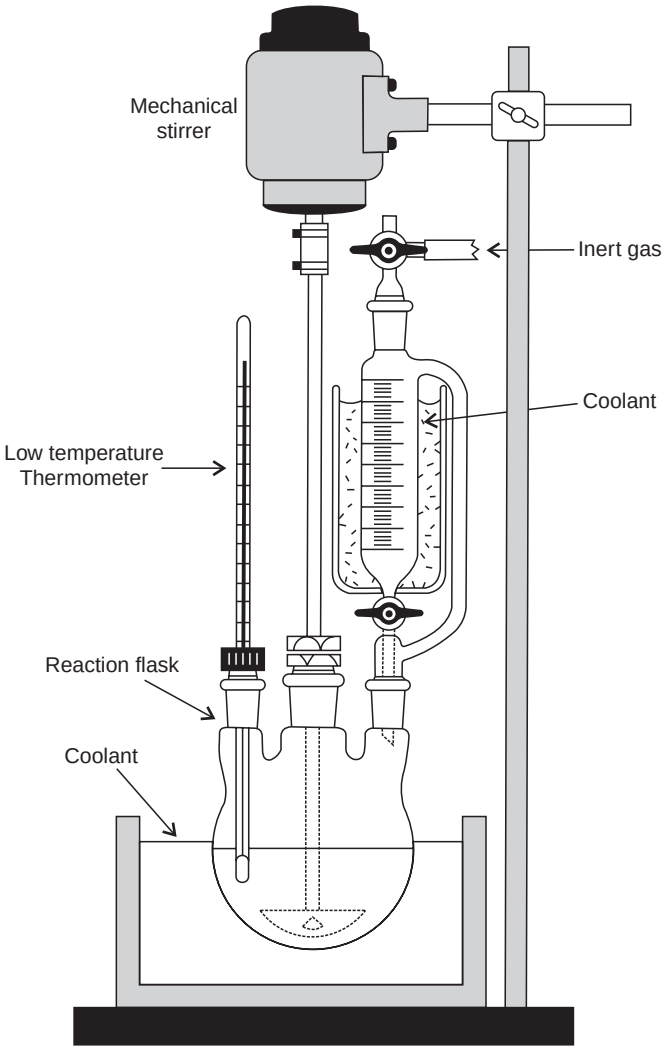

Fig. 3.17. Assembly for reactions on larger scales at low temperature.

In another instance where the reactions on larger scales are required to be performed ; and usual conditions like constant agitation, gentle or vigorous reflux under atmospheric pressure, the standard laboratory equipments are more than adequate and necessary. Fig. 3.18 illustrates a quite common and typical laboratory assembly for a large-scale reflux of reaction mixtures. In this specific instance the provided **pressure equalized dropping funnel** may be refilled by displacing the top stopper and pouring in the desired reactant ; or in case, the material is highly sensitive to atmospheric moisture and relative humidity, consequently the same may be transferred quite effectively right into the dropping funnel *via* a cannula by replacing the glass stopper with an adequate septum.

Heatng may be afforted *via* either a thermostatically controlled heating mantle or a heating bath, as is usually common with a host of other reaction systems. It is, however, pertinent to mention here and is always recommended that the source of heating should be

positioned (mounted) on a laboratory-jack so that it may be removed quickly in case of an emergency situation.

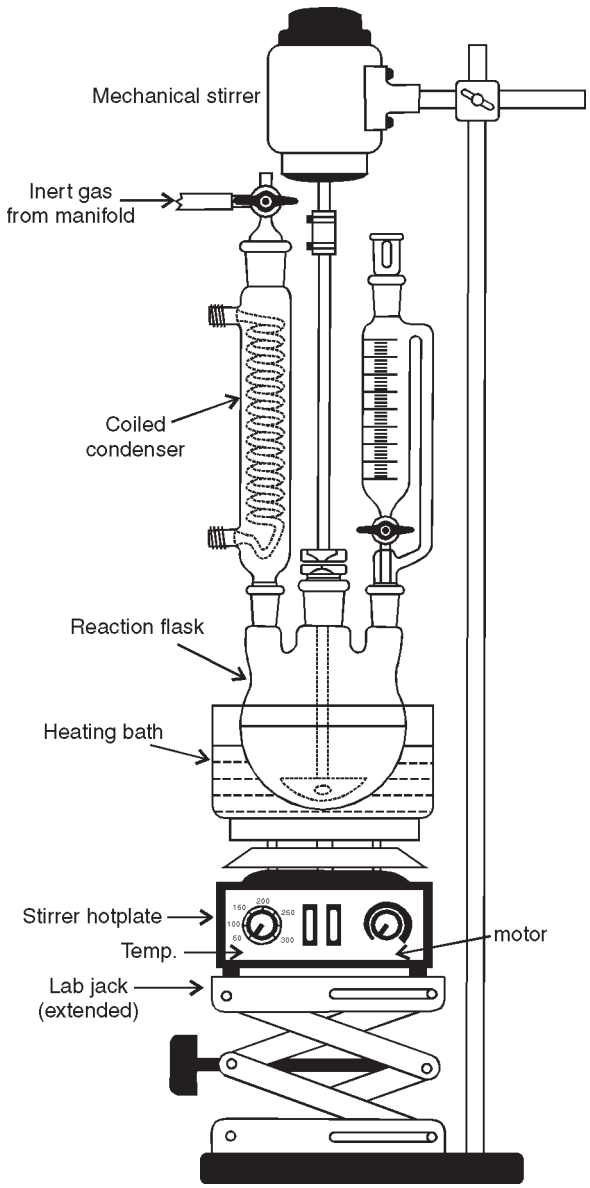

Fig. 18. Assembly for reactions on larger scales to be performed under reflux and agitation.

XIII. Photolysis

Photolysis means dissolution or disintegration under the stimulus of light *i.e.,* ultra-violet rays (radiations).

Caution. The UV-radiation is extremely damaging to the eyes and skin.

Fig. 3.19 duly represents a commonly employed **'photo-chemical reactor'** to carry out **'photolysis'** in a chemical laboratory. However, there are some extremely important precautionary measures that one has to observe and adopt rigidly when performing reactions using a standard **'photochemical reactor'**, namely :

1. The *'photochemical reactor'* should be adequately provided with a *protective screen.*
2. It is absolutely mandatory to put on special protective goggles or more appropriately a complete face shield that certainly caters for still better protection against all sorts of UV-radiations in case the apparatus requires any type of *'adjustment'* (or samples withdrawn) when the **UV-Lamp** is still on.
3. All naked portions of the body *e.g.,* hands, may also be adequately protected with *'prescribed gloves'*. Also one must ensure that no parts of skin should be exposed to radiation in the unfortunate event of an accident. However, it is always advisable and preferable to turn off the UV-Lamp, obviously for safety measures, especially when such manipulations are required to be carried out.

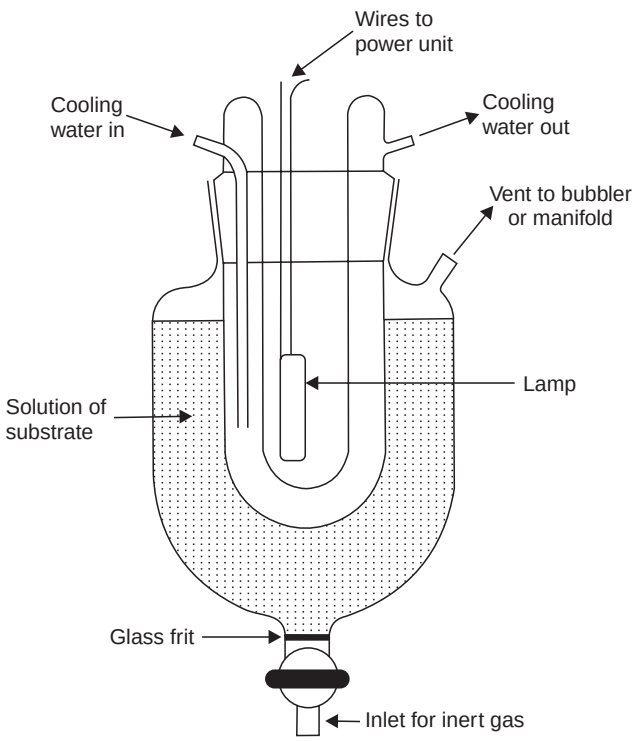

Fig. 3.19. Immersion-well photochemical reactor.

Fig. 3.19 represents an *immersion-well* **'photochemical reactor'** that may be employed for carrying out most of the **preparative photochemical reactions.**

In order to operate an immersion-well photochemical reactor effectively, first of all the air is removed from the solvent by slowly allowing inert nitrogen or argon gas to bubble through it *via* the sintered glass-disk. It is equally important to make sure that the correct choice of lamp is made for the reactor before starting the reaction.

Low pressure lamps emit usually most of their radiations at **254 nm ;** these are of low power (upto ~ 20 W) and hence, require invariably a **Quartz Immersion Well** and not made of **'Pyrex'.** Interestingly, a plethora of *'preparative reactions'* normally makes use of **much higher power** (ranging between 100–400 W) known as the **medium pressure lamps,** as these are found to emit their radiation over a much broader range (mainly at ~ 365 nm with other obtainable bands at both shorter and longer wavelength). It is always preferable to employ a suitable filter which essentially helps to allow a reaction to proceed under the most specified and correct experimental conditions.

Importantly, most photochemical reactions are invariably performed at fairly high dilution *i.e.,* upto ~ 0.05 M ; and extra care must be taken for the selection of pure and appropriate solvent. It must be seen that the **'chosen solvent'** may not undergo decomposition under the influence (exposure) of UV-radiation ; besides, it must not get absorbed to the least possible extent at the particular wavelength that is being employed for the ensuing photochemical reaction. Subsequently, the solvent, needs to be evaporated carefully from the reaction mixture ; and the product is finally purified by crystallization.

RECOMMENDED READINGS

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CHAPTER 4

Syntheses of Medicinal Compounds

4.1 ACETYLATION METHODS

4.1.1 Introduction

The replacement of '*active hydrogen*' of compounds belonging to the class **ROH** (phenols or alcohols), in addition to compounds of the category $\mathbf{RNH_2}$ and $\mathbf{R_2NH}$ (*i.e., primary*- and *secondary*-amines may be acetylated directly, whereby the reactive H-atom is specifically replaced by the **acetyl radical**, $-\overset{\overset{O}{\|}}{C}-CH_3$. This replacement of an *active hydrogen* by an **acetyl function** is termed as **acetylation**.

In true sense, the acetylation of alcohols and phenols is really regarded as a specific instance of **esterification** by virtue of the fact that the resulting *acetyl derivative i.e.,* $R-O-\overset{\overset{O}{\|}}{C}-CH_3$, is, evidently an '*ester*' of acetic acid. Likewise, the primary and secondary amines give rise to the corresponding acetyl derivatives of the type $RNH-\overset{\overset{O}{\|}}{C}-CH_3$ and $R_2N-\overset{\overset{O}{\|}}{C}-CH_3$, respectively, that may be regarded as *mono*- and *di*-substituted derivatives of **acetamide** *i.e.*, $H_2N-\overset{\overset{O}{\|}}{C}-CH_3$.

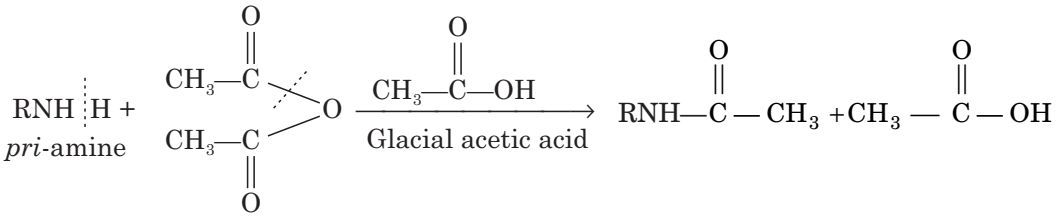
In actual practice, *acetylation* may be accomplished by *two* major procedures, namely :

Procedure–I. *Heating with a mixture of Acetic anhydride and Acetic acid :*

It has been observed that when a primary or secondary amine is reacted with glacial acetic acid by the application of heat, the corresponding acetyl derivative is obtained ; however, the ensuring reaction is invariably found to be extremely sluggish and slow, as given below :

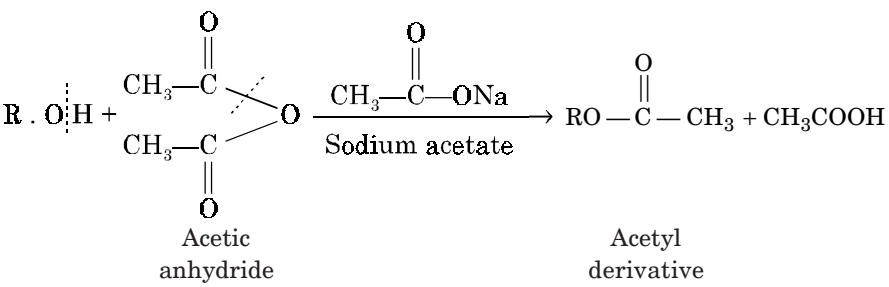
$$RNH\,.\,\boxed{H}+\boxed{HO}-\overset{\overset{O}{\|}}{C}-CH_3 \longrightarrow RNH-\overset{\overset{O}{\|}}{C}-CH_3 + H_2O$$

If, acetic anhydride is mixed with glacial acetic acid in equal proportions (1 : 1) the acetylation proceeds with a remarkable rapid and fast manner, as shown below :



This is due to the fact that acetic anhydride is much more reactive than glacial acetic acid alone ; and the presence of the latter helps the reaction to proceed in the forward direction to knock out a mole of acetic acid.

The primary alcohol on being treated with acetic anhydride in the presence of sodium acetate yields the acetyl derivative (an ester) along with a mole of acetic acid as given below :



The role of sodium acetate is to provide enough acetate ions upon dissociation which would carry out the reaction in the forward direction to generate the corresponding acetyl derivative and acetic acid.

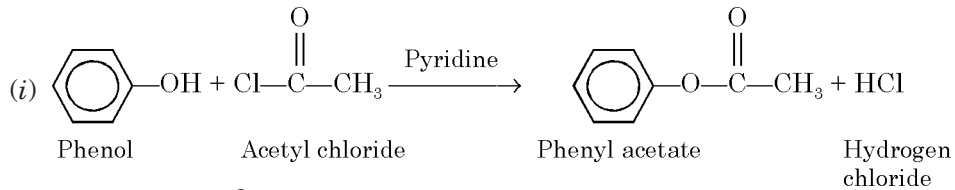
Disadvantage of Using Acetic Anhydride. There are *two* main disadvantages observed when acetic anhydride is employed as an acetylating agent, namely :

(*a*) **Formation of traces of Diacetyl Compound.** The primary amines usually forms traces of the corresponding *diacetyl compound*, $RN\left(\begin{matrix}O\\ \|\\ C-CH_3\end{matrix}\right)_2$; however, the possibilities of this specific secondary acetylation are quite rare and remote. The ultimate recrystallisation of the crude product from an aqueous medium shall broadly hydrolyse the diacetyl derivative back to the mono-acetyl derivative very rapidly.

(*b*) **Addition of a catalyst.** In order to carry out the complete acetylation of *polyhydric chemical entities*, such as : **glucose** and **mannitol**, even pure acetic anhydride is not that useful and effective ; and therefore, the absolute necessity of an appropriate third substance is required as a '**catalyst**', such as : *anhydrous sodium acetate.*

Procedure–II. *Treatment with Acetyl Chloride :*

Acetylation may be caused with the help of acetyl chloride specifically smoothly in the presence of **pyridine** which absorbs the hydrogen chloride formed during the course of reaction almost instantaneously as given below :



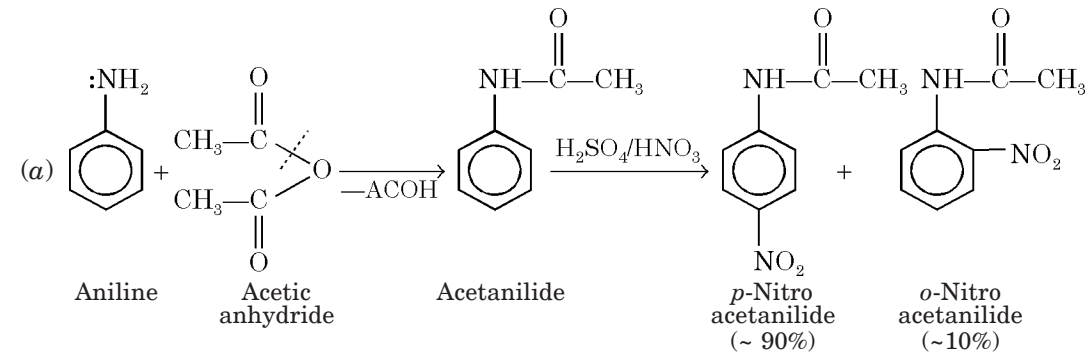
Uses of Acetylation. The following are the major uses of *acetylation reaction,* such as :

(1) For the identification and subsequent characterization of hydroxy compounds as well as primary and secondary amines, by preparing their crystalline acetyl derivatives.

Note : The particular aspect is exclusively applicable to the aromatic compounds because the aliphatic compounds are invariably liquid in nature, and also are frequently miscible in an aqueous medium.

(2) For the **protection** of either a *primary-* or a *secondary-amino moiety* in the course of a chemical reaction.

Example. Preparation of *para*-nitroaniline :

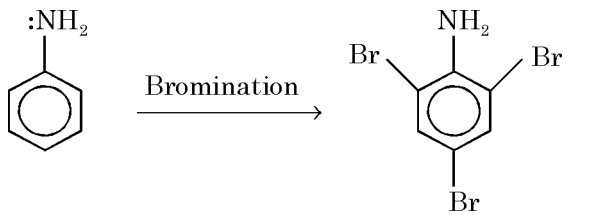


The highly active amino function present in aniline is duly protected by acetylating it with acetic anhydride to obtain **acetanilide** and the elimination of a mole of acetic acid. The acetanilide is now subjected to nitration by concentrated sulphuric acid and fuming nitric acid to obtain the *two* products, namely : *para*-nitro acetanilide (~ 90%) and *ortho*-nitro acetanilide (~ 10%).* Finally, the *para*-nitroaniline is obtained by carrying out the hydrolysis of the corresponding *p*-nitro acetanilide with 70% sulphuric acid.

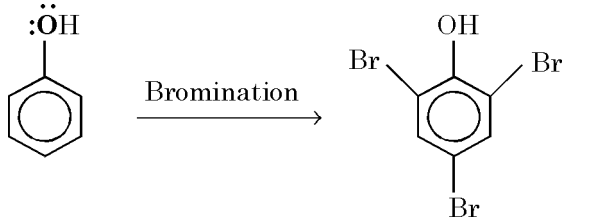
(3) For the preparation of *mono-substituted derivatives* of the *aromatic amines* or *phenols.* It is, however, pertinent to mention here that the mono-substituted derivatives of these compounds cannot be prepared directly by the interaction of suitable reagent due to the highly activating influences of these functional groups.

Examples. The following *two* examples expatiate the above observations, namely :

(*a*) Direct **bromination** of either *aniline* or *phenol* gives rise to **tribromoaniline** or **tribromophenol** respectively, as shown below :

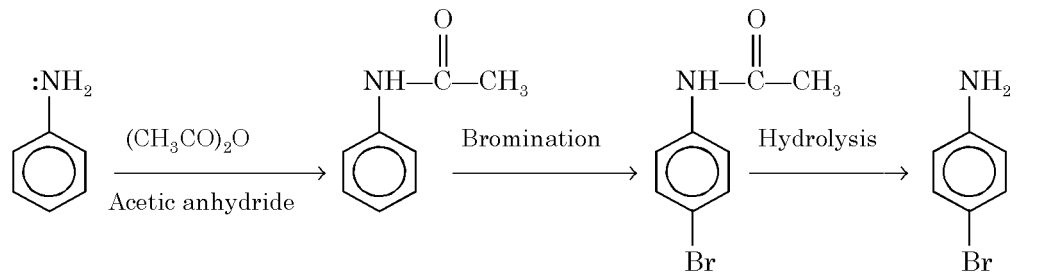


Aniline — 2, 4, 6-Tribromoaniline



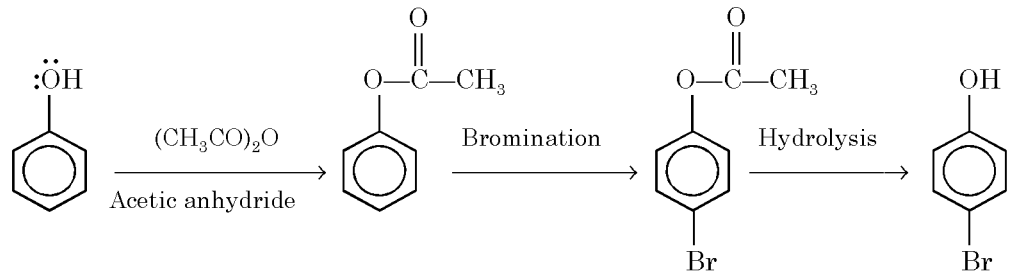
Phenol — 2, 4, 6-Tribromophenol

In the event, when either the *free amino function* of aniline or the *free hydroxyl function* of phenol, is first **protected** by acetylation, and subsequently the bromination is carried out one may get the **mono-substituted bromo derivative** after hydrolysis of the resulting product, as illustrated below :



Aniline — Acetanilide — *para*-Bromo-acetanilide — *para*-Bromo-aniline

* The acetamido $\left(\begin{matrix} \text{O} \\ \| \\ i.e., \text{NH} - \text{C} - \text{CH}_3 \end{matrix} \right)$ function is an *ortho*- and *para*-directing group.



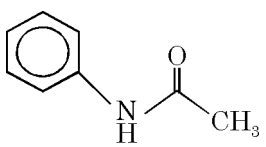
Note : Acetyl derivatives of most of the amines and phenols are obtained as crystalline compounds having definite melting points. Hence, the corresponding derivatives may be used as a means for the characterization of the parent compounds.

4.1.2 Syntheses of Medicinal Compounds

The following sections shall exclusively deal with the elaborated syntheses of certain **medicinal compounds** prepared by using the **acetylation methods**, such as : Acetanilide, Acetylsalicylic acid (Aspirin) ; Acetylacetone ; Phenacetin, Acetylcysteine ; and Paracetamol.

4.1.2.1 Acetanilide :

4.1.2.1.1 Chemical Structure :



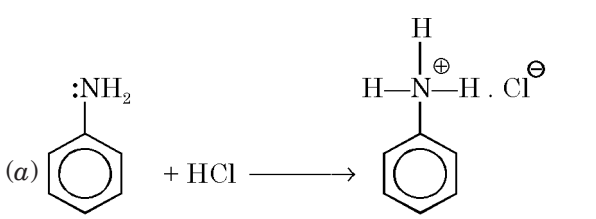
Acetanilide

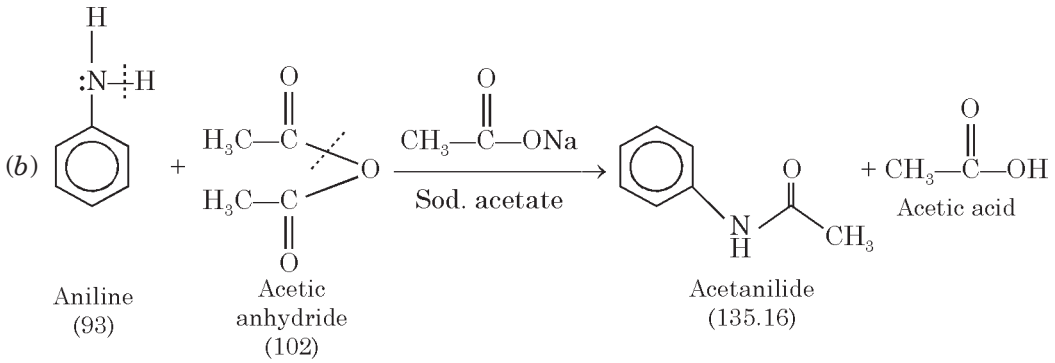
4.1.2.1.2 Synonyms. N-Phenylacetamide ; Antifebrin ; Acetylaniline ; Acetylaminobenzne.

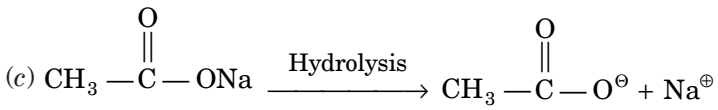
Acetanilide may be prepared by the following **two** methods :

4.1.2.1.2.1 (Method–I). It is prepared from aniline, acetic anhydride, sodium acetate and concentrated hydrochloric acid (12 N).

4.1.2.1.2.2 Theory :







The freshly redistilled aniline, is almost a colourless oily liquid which being practically insoluble in water. Therefore, before carrying out the **'acetylation'** aniline has got to be made soluble in the aqueous medium. It can be accomplished by adding requisite amount of concentrated HCl whereby the highly reactive amino function easily takes up a proton from the dissociation of HCl in water, get protonated to yield aniline hydrochloride that is water-soluble. Subsequently, the soluble form of aniline is reacted with acetic anhydride in the presence of sodium acetate. The acetate ion obtained from the hydrolysis of the salt (sodium acetate) helps to sustain the acetylation reaction in the forward direction to yield acetanilide completely.

4.1.2.1.2.3 Chemicals Required. (*i*) Aniline : 10 ml (Freshly redistilled to have almost a colourless product) ; (*ii*) Acetic anhydride : 13 ml ; (*iii*) Sodium acetate (crystalline) : 16.5 g ; and (*iv*) Concentrated Hydrochloric acid (12 N) : 9 ml.

4.1.2.1.2.4 Procedure. The various steps involved are as follows :

(1) Transfer 10 ml of aniline is a 500 ml beaker and add to it 9 ml of concentrated hydrochloric acid and 25 ml of distilled water. Stir the contents of the beaker thoroughly with a glass rod till the whole of aniline undergoes dissolution.

(2) Dissolve in a separate 100 ml beaker 16.5 g of sodium acetate in 50 ml of distilled water.

(3) To the clear solution of aniline (1), add 13 ml of acetic anhydride, in small lots at intervals, with constant vigorous stirring until a perfect homogeneous solution is obtained.

(4) **Immediately** pour the solution obtained from (3) into the sodium acetate solution (2). Shake the contents thoroughly with the help of a glass rod and immerse the beaker containing the reactants in an ice-bath.*

(5) Beautiful shining crystals of **Acetanilide** separate out which may be filtered at the Büchner funnel by applying suction, washed with enough cold water, squeeze out the

*__Ice-Bath.__ A small tray, made up of HDPE, containing crushed ice duly sprinkled with powdered crude sodium chloride, usually known as a Freezing Mixture.

excess of water by pressing with an inverted glass stopper. Transfer the crude product onto a watch glass with the aid of a stainless-steel spatula and finally dry it in an electric oven previously maintained at 80°C. The yield of crude acetanilide (mp 113–114°C) is approximately 12 g.

4.1.2.1.2.5 Precautions :

1. Always use freshly redistilled '**aniline**' to obtain better product and also proper yield.

2. Sodium acetate must be crystalline and pure.

4.1.2.1.2.6 Recrystallization. Recrystallization is invariably afforded by dissolving the product in the minimum quantity of the solvent. In this case, take about 2 g of the crude acetanilide obtained from section 4.1.2.1.2.4, and dissolve it in minimum volume of hot rectified spirit [2% (*v*/*v*)]. Practically snow-white crystals of acetanilide are obtained.

4.1.2.1.2.7 Theoretical yield/Practical yield. The theoretical yield may be calculated from Eq. (*b*) under theory (section 4.1.2.1.2.2) as follows :

93 g of aniline on reacting with 102 g of acetic anhydride

yields acetanilide = 135.16 g

10 g of aniline* shall yield acetanilide $= \frac{135.16}{93} \times 10 = 14.5$ g

Therefore, Theoretical yield of Acetanilide = **14.5 g**

Reported Practical yield = 12 g

Hence, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{12}{14.5} \times 100 =$ **82.75**

4.1.2.1.2.8 Physical Parameters. It is obtained as orthorhombic plates, scales from water, having mp 113–115°C, bp 304–305°C, slightly burning taste, appreciably volatile at 95°C, d_4^{15} 1.219 g , K_b at 28°C 1×10^{-13}. 1 g dissolves in 185 ml water, 20 ml of boiling water, 3.4 ml ethanol, very sparingly soluble in petroleum ether, and chloroform enhances the solubility of acetanilide in water.

4.1.2.1.2.9 Uses :

(1) It possesses antipyretic and analgesic activities.

(2) It is invariably used in the manufacture of other medicinals *e.g.*, sulphonamide ; besides dyes.

(3) It is also employed as a stabilizer for H_2O_2 solution.

(4) It finds its application as an additive to cellulose ester varnishes.

4.1.2.1.2.10 Questions for *Viva-Voce* :

(1) Why is freshly distilled aniline always preferred in the synthesis of acetanilide ?

(2) How does hydrochloric acid help to solubilize oily aniline in an aqueous medium ?

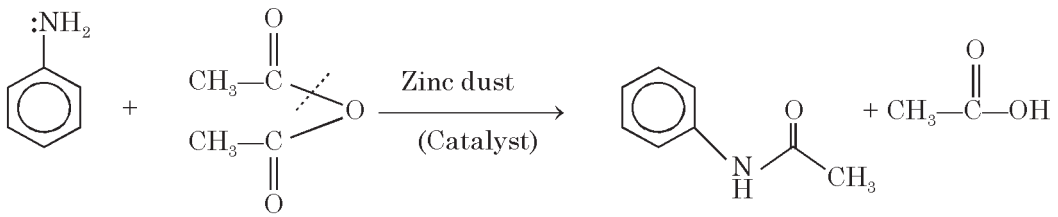
[*% d_{20}^{20} = 1.022 for aniline].

(3) What is the role of sodium acetate in this reaction ?

(4) Why is the 'practical yield' always lesser than the 'theoretical yield' ?

4.1.2.1.2.2 (Method–II). It is prepared from aniline, acetic anhydride, glacial acetic acid and zinc dust.

4.1.2.1.2.2.1 Theory :



In this instance, a mixture of acetic anhydride and glacial acetic acid (1 : 1) serves as an alternative acetylating agent in the presence of zinc dust as a catalyst. Acetic acid undergoes dissociation to provide acetate ion (CH_3COO^-) which helps in the cleavage of acetic anhydride molecule to augment the formation of acetanilide and liberate another molecule of acetic acid which is being used up in the above reaction once again.

4.1.2.1.2.2.2 *Chemicals Required*. (*i*) Aniline : 10 ml (Freshly redistilled colourless product) ; (*ii*) Acetic anhydride : 10 ml ; (*iii*) Glacial acetic acid : 10 ml ; and (*iv*) Zinc dust : 0.5 g.

4.1.2.1.2.2.3 Procedure. The various sequential steps involved are as stated below :

(1) Place 10 ml of aniline together with 10 ml glacial acetic acid, 10 ml acetic anhydride and 0.5 g zinc dust in a 250 ml round bottomed flask fitted with a reflux condenser.

(2) Heat the reaction mixture to boiling for 30–40 minutes on a heating mantle, detach the condenser, and transfer the hot contents **carefully** into a 500 ml beaker containing 250 ml cold water in small lots at intervals with constant vigorous stirring with a glass rod. (**Note : Care should be taken to prevent any residual zinc powder being transferred into the beaker.**)

(3) Cool the contents of the beaker by placing it in an ice-both when the orthorhombic plates of acetanilide start separating out gradually.

(4) Filter the crude product in a Büchner funnel using suction, wash with cold water, squeeze out the remaining water by pressing with an inverted glass stopper, and fianally dry it in an oven maintained at 80°C. The yield of crude acetanilide (mp 113–114°C) is approximately 13.5 g.

4.1.2.1.2.2.4 Precautions :

(1) Freshly redistilled **'aniline'** should always be used for better product, and also a better yield.

(2) Residual zinc dust must be avoided while pouring the reacted contents from the flask into the beaker containing cold water.

4.1.2.1.2.2.5 Recrystallization. Please follow the same procedure as stated under section 4.1.2.1.2.6.

4.1.2.1.2.2.6 Theoretical yield/Practical yield :

$$\text{Percentage Practical yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

$$= \frac{13.5}{14.5} \times 100 = \mathbf{93.10}$$

The physical parameters and uses are identical with those given under sections 4.1.2.1.8. and 4.1.2.1.9.

4.1.2.1.2.2.7 Questions for *Viva-Voce* :

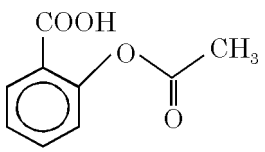
(1) How does acetic acid help in the 'acetylation' of aniline ?

(2) Does the acetylation of aniline **'protect'** the free amino group ?

(3) Give the name of a **'class of compound'** that may be prepared from acetanilide.

4.1.2.2 Aspirin :

4.1.2.2.1 Chemical Structure



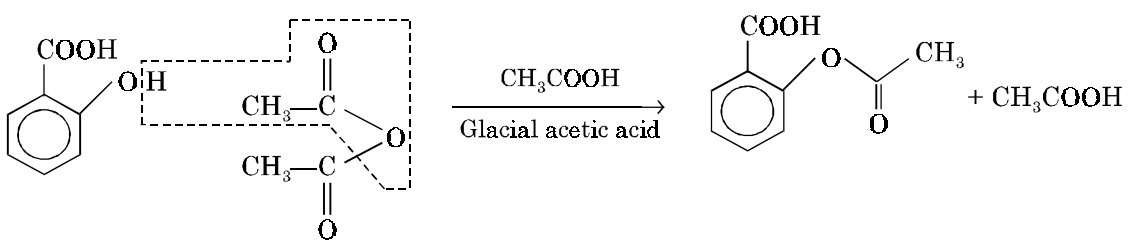
Aspirin

4.1.2.2.2 Synonyms. Acetylsalicylic acid ; Acetophen ; Acetosal ; Acetylin ; Acetyl–SAL ; ASA ; Acylpyrin ; Arthrisin ; Asatard ; Caprin ; Duramax : Entrophen ; Saletin ; Solpyron ; Xaxa.

Aspirin may be prepared by any one of the following **three** methods :

4.1.2.2.2.1 (Method–I). It is prepared from salicylic acid, acetic anhydride and glacial acetic acid.

4.1.2.2.2.2 Theory



Salicylic acid (138) | Acetic anhydride (102) | Aspirin (180)

Salicylic acid interacts with acetic anhydride in the presence of glacial acetic acid whereby the cleavage in acetic anhydride takes place with the formation of aspirin and a mole of acetic acid. The glacial acetic acid helps in the generation of excess acetate ion which carries the reaction in the forward direction. The acetic acid obtained as a product of reaction is reused in the reaction itself.

4.1.2.2.2.3 Chemicals Required. (*i*) Salicylic acid : 6 g ; (*ii*) Acetic anhydride : 10 ml ; and (*iii*) Glacial acetic acid : 10 ml.

4.1.2.2.2.4 Procedure. The following steps may be adopted in a sequential manner :

(1) Prepare an admixture of 10 ml each of acetic anhydride and glacial acetic acid in a 100 ml clean and dry beaker.

(2) Now, add this mixture carefully to 6 g salicylic acid previously weighed and placed in a 100 ml round bottom flask ; and fit the same with a reflux condenser.

(3) Boil the reaction mixture on an electric heating mantle for a duration of 35–45 minutes.

(4) Pour the hot resulting mixture directly into 100 ml cold water, contained in a 500 ml beaker in one lot ; and stir the contents vigorously with a clean glass rod when the shining tiny crystals of aspirin separate out.

(5) Filter off the crude aspirin in a Büchner funnel fitted with an air-suction device and wash the residue with sufficient **cold water**, drain well and finally remove the excess of water by pressing it between the folds of filter paper and spread it in the air to allow it dry completely. However, it may also be dried expeditiously by drying it in an electric oven maintained at 100°C for about an hour. The yield of crude aspirin (mp 133.5–135°C) is approximately 7.5 g.

4.1.2.2.2.5 Precautions :

(1) All glass apparatus to be used in the synthesis must be perfectly dried in an oven.

(2) Gentle refluxing should be done to complete the acetylation of salicylic acid.

4.1.2.2.2.6 Recrystallizatoin. Recrystallize the crude product from a mixture of acetic acid and water (1 : 1). The yield of pure colourless aspirin (mp 13.4°C) is 7.25 g.

4.1.2.2.2.7 Theoretical yield/Practical yield. The theoretical yield is usually calculated from the equation under theory (section 4.1.2.2.2.2) as stated under :

138 g of salicylic acid on reacting with 102 g of acetic anhydride

yields Aspirin = 180 g

$\therefore$ 6 g of salicylic acid shall yield Aspirin $= \frac{180}{138} \times 6 = 7.82$ g

Hence, Theoretical yield of Aspirin = **7.82 g**

Reported Practical Yield = 7.5 g

Therefore, Percentage Practical Yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{7.5}{7.82} \times 100 =$ **95.90**

4.1.2.2.2.8 Physical Parameters. Aspirin is obtained as monoclinic tablets or needle-like crystals, mp 135°C (rapid heating) ; the melt gets solidified at 118°C ; uv_{max} (0.1 NH_2SO_4) : 229 nm ($E^{1\%}_{1\,cm}$ 484) ; $CHCl_3$: 277 nm ($E^{1\%}_{1\,cm}$ 68). It is usually odourless, but in moist air it gets hydrolyzed slowly into salicylic acid and acetic acid, and overall acquires the odour of acetic acid. It is fairly stable in dry-air, 1 g dissolves in 300 ml water at 25°C, in 100 ml of water at 37°C, in 5 ml ethanol, 17 ml chloroform and 10–15 ml solvent ether.

4.1.2.2.2.9 Uses :

(1) It is used for the relief of minor aches and mild to moderate pain.

(2) It is recommended for arthritis and related arthritic conditions.

(3) It is also indicated for myocardial infarction prophylaxis.

(4) It is employed to reduce the risk of transient ischemic attacks in men.

4.1.2.2.2.10 Questions for *Viva-Voce* :

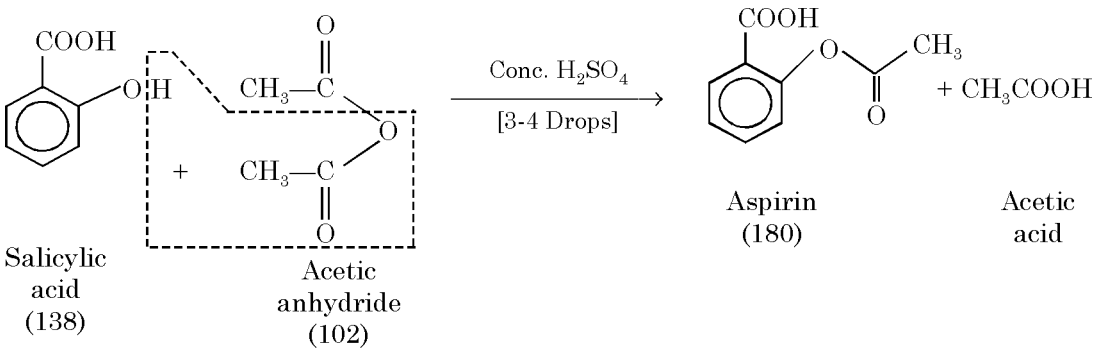
(1) Why is it necessary to recrystallize aspirin before being used as a medicine ?

(2) Why aspirin must be stored in dry air or air-tight containers ?

(3) What is the role of acetic acid in the reaction between salicylic acid and acetic anhydride ?

4.1.2.2.2.2 (Method–II). Aspirin may also be prepared from salicylic acid, acetic anhydride and a few drops of concentrated sulphuric acid.

4.1.2.2.2.2.1 Theory



Salicylic acid (138) — Acetic anhydride (102) — Aspirin (180) — Acetic acid

Salicylic acid interacts with acetic anhydride in the presence of a few drops of concentrated sulphuric acid to produce aspirin and a molecule of acetic acid. The purpose of adding conc. sulphuric acid* is to aid and augment the process of detaching the acetate ion $\left[CH_3—\overset{\overset{O}{\|}}{C}—C^{\ominus}\right]$ from acetic anhydride which ultimately gets associated with the H^+ ion from the phenolic hydroxy group in salicylic acid to be eliminated as a mole of acetic acid.

4.1.2.2.2.2.2 Chemicals Required : (1) Salicylic acid : 6 g ; (2) Acetic anhydride : 8.5 ml ; and (3) Conc. Sulphuric acid : 3–4 drops.

4.1.2.2.2.2.3 Procedure. The various steps involved are :

(1) Weigh 6 g of salicylic acid and transfer to a 100 ml clean and dry conical flask.

(2) Add to the flask 8.5 ml of acetic anhydride and 3–4 drops of concentrated sulphuric acid carefully.

(3) Mix the contents of the flask thoroughly ; and warm the mixture on a water-bath maintained at 60°C for about 15–20 minutes with frequent stirring.

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*__Sulphuric Acid.__ Acts as **'catalyst'**.

(4) Allow the contents of the flask to cool down to ambient temperature, and pour it in a thin stream into 100 ml of cold water in a 250 ml beaker with constant stirring.

(5) Filter the crude product on a Büchner funnel using suction, wash it generously with **cold water**, drain well and dry between the folds of filter paper or in an oven maintained at 90°C. The yield of crude aspirin (mp 133–134°C) is about 7.75 g.

4.1.2.2.2.2.4 Precautions :

(1) All glass apparatus that are used in the synthesis must be absolutely dry.

(2) Concentrated sulphuric acid should be added very cautiously into the reaction mixture.

(3) The reaction mixture is to be warmed only at 60°C for 20 minutes.

4.1.2.2.2.2.5 Recrystallization. The same procedure as stated under section 4.1.2.2.2.6 may be adopted.

4.1.2.2.2.2.6 Theoretical yield/Practical yield. It is almost identical to the one mentioned under section 4.1.2.2.7.

The '*Physical Parameters*' and the '*Uses*' are same as stated under Method I (sections 4.1.2.2.2.8 and 4.1.2.2.2.9).

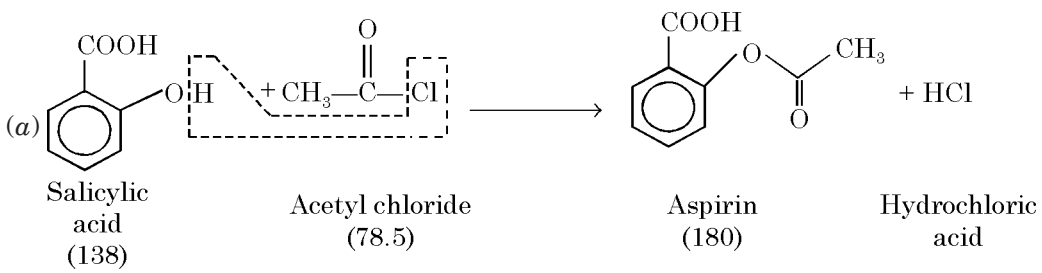
4.1.2.2.2.2.7 Questions for *Viva-Voce*

(1) Why is the amount of acetic anhydride used in *Method II* for the same quantity of salicylic acid is 1.5 ml less than *Method I* ?

(2) What is the specific role played by a few drops of concentrated sulphuric acid ?

4.1.2.2.2.3 (Method–III). Aspirin may also be synthesized by the interaction of salicylic acid with acetyl chloride (*i.e.*, on acid chloride) in the presence of pyridine which being a weak base rapidly forms salts with strong acids.

4.1.2.2.2.3.1 Theory :



The interaction between salicylic acid and acetyl chloride gives rise to the formation of aspirin *i.e.*, the acetylated product with the elimination of **one** mole of HCl. The liberated mineral acid *i.e*., HCl, being a strong acid readily reacts with pyridine (a weak base) in the reaction mixture to form the corresponding salt *i.e.*, pyridine hydrochloride.

4.1.2.2.2.3.2 Chemicals Required. (1) Salicylic acid : 6 g ; (2) Acetyle chloride : 5 ml ; (3) Pyridine : 5 ml.

4.1.2.2.2.3.3 Procedure. The following steps are to be followed sequentially :

(1) Transfer 6 g of salicylic acid in a 150 ml conical flask and add to it 5 ml of pure redistilled pyridine.

(2) Place the above conical flask in an ice-bath and chill the contents to approximately 5–7°C.

(3) Transfer exactly 5 ml of acetyl chloride in a 50 ml dropping funnel and add it **drop-wise very slowly** into the solution of salicylic acid with constant and vigorous stirring.

(4) After the absolute addition of acetyl chloride, the contents of the conical flask was heated over a water-bath for a duration of 5–10 minutes so as to allow the reactions (*a*) and (*b*) to near completion.

(5) Cool the contents of the flask when a semi-solid residue is obtained, to which 50 ml of water and a few chips of ice are added with frequent stirring/swirling.

(6) The crude aspirin is filtered on a Büchner funnel with suction, washed with cold water, drained well and dried either between the folds of filter paper or dried in an oven maintained below 95°C. The yield of crude aspirin (mp 133–135.5°C) is 7.6 g.

4.1.2.2.3.4 Precautions

(1) Pyridine must be redistilled before use in this preparation.

(2) Step (3) above is exothermic in nature ; hence, the addition of acetyl chloride should be both gradual and vigorous stirring required.

(3) Subsequent heating of the reaction mixture after complete addition of acetyl chloride is an absolute necessity.

4.1.2.2.2.3.5 Recrystallization. The same procedure as stated under section 4.1.2.2.2.2.6 should be adopted.

4.1.2.2.2.3.6 Theoretical yield/Practical yield. The theoretical yield is calculated from equation (*a*) under theory section 4.1.2.2.2.3.1 as given below :

138 g of salicylic acid when reacted with 78.5 g of acetyl chloride

shall yield Aspirin = 180 g

$\therefore$ 6 g of salicylic acid shall yield Aspirin $= \frac{180}{138} \times 6 = 7.82$ g

Hence, Theoretical yield of Aspirin = **7.82 g**

Reported Practical Yield = 7.6 g

Therefore, Percentage Practical Yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100 = \frac{7.6}{7.82} \times 100 =$ **97.18**

However, the '*Physical Parameters*' and the '*Uses*' are same as stated under Method–I (sections 4.1.2.2.2.8 and 4.1.2.2.2.9).

4.1.2.2.2.3.7 Questions for *Viva-Voce* :

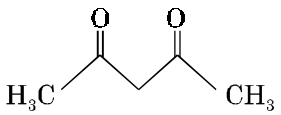
(1) Why is the quantity of acetyl chloride just one half than the quantity of acetic anhydride used in Method–I and Method–II ?

(2) What is the crucial role played by '*pyridine*' in the method of acetylation ?

(3) Why is acetyl chloride added gradually to an ice-cold mixture of salicylic acid and pyridine ?

4.1.2.3 Acetylacetone :

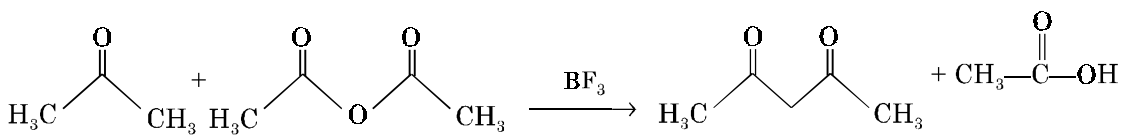
4.1.2.3.1 Chemical Structure :



Acetylacetone

4.1.2.3.2 Synonyms. Diacetylmethane ; 2, 4-Pentanedione ; Pentane-2, 4-dione.

4.1.2.3.3 Theory



Acetone (58) Acetic Anhydride (102) Acetylacetone (100)

The interaction between acetone and acetic anhydride yields acetylacetone in the presence of boron trifluoride* which acts as an *acylation catalyst* ; and acetic acid is obtained as a by product. Acetylacetone is precipitated as its corresponding copper-complex by the addition of cupric acetate solution. Subsequently, acetylacetone is regenerated by treatment with diluted sulphuric acid and extracted successively with solvent ether.

4.1.2.3.4 Chemical Required. (1) Pure anhydrous Acetone : 5.8 g (7.3 ml, 1 mol) ; (2) Acetic anhydride : 25.5 g (23.6 ml ; 2.5 mol) ; (3) Boron trifluoride : 25 g ; (4) Crystallized sodium acetate : 40 g ; (5) Pure crystallized cupric acetate : 12 g ; (6) Sulphuric acid (20% w/w) : 40 ml ; (7) Ether solvent : 40 ml ; and (8) Anhydrous sodium sulphate : 12.5 g.

4.1.2.3.5 Procedure. The different steps followed in the synthesis of acetylacetone are as described below :

(1) A 3-necked 500 ml round-bottom (RB) flask is fitted with a gas-inlet tubing and a gas-outlet tubing leading to a *gas- absorption-* device (see Chapter 3) charged with an aqueous alkali solution so as to trap the excess of BF_3 gas ; and lastly stopper the third neck.

*Meerwein and Vossen, *J. Prakt*. Chem., 141, 149 (1934).

(2) Place 5.8 g (7.3 ml, 1 mol) of pure anhydrous acetone* and 25.5 g (23.6 ml, 2.5 mol) of acetic anhydride in the RB flask ; and cool the contents in an ice-bath containing a freezing mixture of *ice and salt.***

(3) Now, connect the gas-intel tubing through a clean and empty wash-bottle to a filled cylinder of commercial boron trifluoride*** ; and allow the gas (BF_3) to bubble through the reaction mixture, *at the rate of 2 bubbles per second,* so that 2.5 g is absorbed in about 65–75 minutes duration.

(4) Pour the reaction mixture in a 500 ml RB flask containing a solution of 40 g of crystallized sodium acetate in 80 ml of water.

(5) The resulting mixture is steam-distilled (see Chapter 3) and collect the distillate in the following proportions : 150 ml, 75 ml and 75 ml.

(6) Separately prepare a solution of 12 g of pure crystallized cupric acetate in 150 ml of water and warm it to about 85°C ; in case the solution is not clear add a few ml of glacial acetic acid.

(7) Precipitate the copper complex of acetylacetone by adding 75 ml of the hot cupric acetate solution to the first collected portion of the steam-distillate ; 45 ml to the second and 30 ml to the third portion. Allow the three separate flasks labelled, I, II and III, preferably kept overnight in the ice-chest.

(8) Filter off the precipitated salt on the Büchner funnel, wash once with water and suck as dry as possible.

(9) Transfer the collected *copper complex* to a separatory funnel, add 40 ml of 20% (w/v) of H_2SO_4 and 40 ml of ether, and shake gently. Remove the ethereal layer.

(10) Extract the aqueous layer with two successive 15 ml portions of ether. Combine the ethereal extracts, dry it with 12.5 g of anhydrous sodium sulphate, and distill off the ether.

(11) Distil the residue through a short-fractionating column and collect the **acetylacetone** at 134–136°C. The yield is approximately 8.0 g (≃ 80%).

4.1.2.3.6 Precautions :

(1) In case, a very dry **'acetylacetone'** is required, acetone must be dried over anhydrous K_2CO_3 or anhydrous $CaSO_4$, followed by P_2O_5.

(2) Boron Trifluoride (commercial grade) may be purchased in cylinders from various suppliers ; and it should be used with **Great Caution**.

***Acetone** is heated under reflux with successive amounts of $KMnO_4$ until the violet colour persists. It is subsequently dried with anhydrous K_2CO_3 or anhydrous $CaSO_4$, filtered from the desiccant and fractionated. **Care should be taken to exclude moisture**.

**When NaCl is dissolved in water, the freezing point of the latter (*i.e.,* water) is depressed ; and their depression being directly propotional to the number of molecules of the solute (NaCl) in unit weight of the solvent (water).

*****BF_3** : It is a colourless gas having pungent and suffocating odour ; and forms dense white fumes in moist air. (**Caution : Potential symptoms of overexposure are nasal irritation, burns to eyes and skin.**)

(3) The **Widmer Column** to be used should have essentially a spiral 15 cm in length, 13 mm, in diameter, and with 15 turns of the helix.

4.1.2.3.7 Redistillation. As the final product, acetylacetone, is already passed through a small-fractionating column ; hence, it is sufficiently pure and need not be redistilled.

4.1.2.3.8 Theoretical yield/Practical yield. The theoretical yield is calculated from equation under section 1.2.3.3. as stated below :

58 g of Acetone when reacted with 102 g of acetic anhydride

will yield acetylacetone = 100 g

$\therefore$ 5.8 g of acetone shall yield acetylacetone $= \frac{100}{58} \times 5.8 = 10$ g

Hence, Theoretical yield of Aspirin = **10 g**

Reported Practical yield = 8.0 g

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{8}{10} \times 100 = \mathbf{80}$

4.1.2.3.9 Physical Parameters. It is mostly obtained as colourless or slightly yellow, flammable liquid having a pleasant odour. It has *d* 0.976, bp 140.5°C, n_D^{20} 1.4512. 1 g dissolves in about 8 g of water. Miscible with ethanol, benzene, chloroform, ether, acetone and glacial acetic acid.

4.1.2.3.10 Uses. It readily forms a good number of organometallic complexes that are mostly used as **fungicides** and as **insecticides**.

4.1.2.3.11 Questions for *Viva-Voce*

(1) Why is it necessary to render the **'Acetone'** to absolute anhydrous condition for the synthesis of acetylacetone ?

(2) Why is it required to cause induction of BF_3 into the reaction mixture at the rate of two bubbles per second ?

(3) What is the importance of BF_3 in this synthesis ?

(4) Why do we have to add glacial acetic acid in preparing a clear solution of Cu(II) acetate in water ?

(5) What is the role played by Cu(II) acetate in the synthesis of **acetylacetone** ?

(6) Why do we use **anhydrous** Na_2SO_4 in the combined ethereal extract before subjecting it to fractional distillation ?

(7) How is the **acetylacetone** regenerated from the **'copper-complex'** ?

4.1.2.3.12 Other Methods of Synthesis. Acetylacetone has also been prepared by several other methods of synthesis, namely :

(*a*) *Condensation* of acetone with ethyl acetate in the presence of **sodium amide**,*

(*b*) *Condensation* of acetone with **alkali or alkaline-earth hydrides**,**

*Adams and Hauser, *J. Am. Chem. Soc.*, **66**, 1220 (1944).

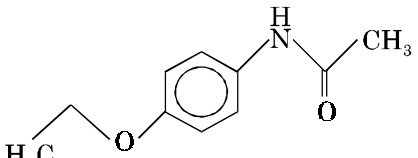
U.S. Pat. 2, 158, 071 [C.A. **33, 6342 (1939)].

(*c*) *Pyrolysis* of **isopropenyl acetate**,* and

(*d*) *Dehydrogenation* of *4-pentanol-2-one* in the presence of **Raney-Nickel.****

4.1.2.4 Phenacetin :

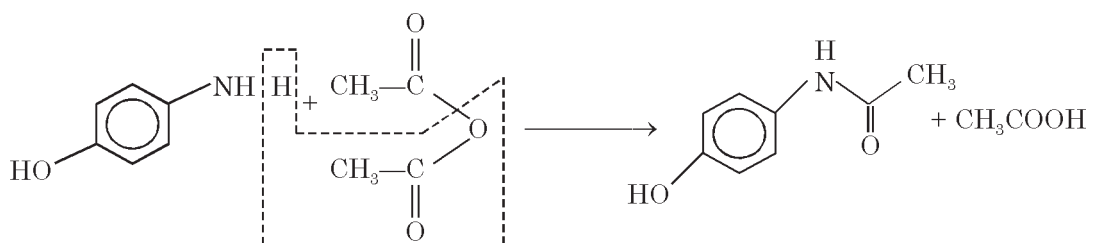
4.1.2.4.1 Chemical Structure :



Phenacetin

4.1.2.4.2 Synonyms. N—(4-Ethoxyphenyl) acetamide ; *p*-Ethoxyacetanilide ; Acetophentidin ; *para*-Acetphenetidin ; *p*-Acetophenetidide.

4.1.2.4.3 Theory [Part–1] :



para-Aminophenol (109.13) | Acetic anhydride (102) | *para*-Acetyl aminophenol (151.13) | Acetic acid (60)

para-Aminophenol on acetylation with acetic anhydride yields the corresponding *para*-acetyl aminophenol and a mole of acetic acid.

4.1.2.4.4 Chemicals Required. (1) *p*-Aminophenol : 5.5 g ; (2) Acetic anhydride : 6 ml.

4.1.2.4.5 Procedure. The various steps involved are as follows :

(1) In a 150 ml conical flask suspend 5.5 g of *p*-aminophenol (0.1 mol) in 15 ml of water, and add to it 6 ml (0.127) mol) of acetic anhydride.

(2) Shake or stir the contents of the flask vigorously and gently warm on a water-bath for about 15–20 minutes with frequent swirling till the solid gets dissolved completely to obtain a clear solution.

(3) Cool the contents, filter the solid acetylated product on a Büchner funnel at the pump, and wash the solid residue with a little cold water to flush out the adhering impurities, if any.

(4) Recrystallize the whole of the crude product obtained in (3) from 40 ml of hot water and finally dry upon filter paper in the air. The yield of *para*-acetylaminophenol, mp 168–169°C, is 7 g (93%).

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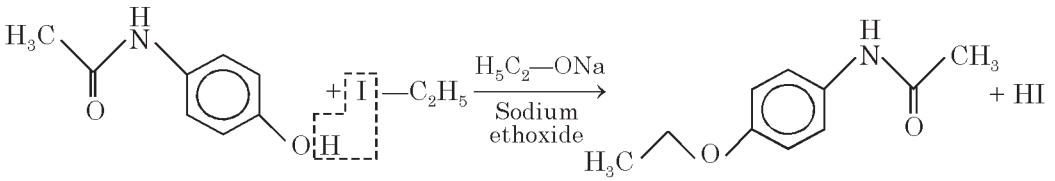
*Hagmeyer and Hull, *Ind. Eng. Chem.*, **41**, 2920 (1949).

DuBois, *Compt, rend.,* **224, 1734 (1947).

4.1.2.4.6 Theory [Part–II] :



para-Acetyl aminophenol (151.13) — Ethyl iodide (156) — Phenacetin (179.22) — Hydroiodic acid (128)

The *para*-acetylaminophenol when reacted with ethyl iodine in the presence of freshly prepared sodium ethoxide gives rise to phenacetin with the liberation of one mole of hydroiodic acid.

4.1.2.4.7 Chemicals Required. (1) *para*-Acetylaminophenol (From Part–I) : 5 g ; (2) Ethyl iodide : 4 ml ; (3) Absolute Ethanol : 20 ml ; (4) Sodium metal : 0.8 g.

4.1.2.4.8 Procedure. The different sequential steps adopted in the synthesis are as follows :

(1) Dissolve 0.8 g freshly cut pieces of sodium metal in 20 ml of absolute ethanol taken in a 250 ml round-bottom flask previously fitted with a reflux condenser. (**Note : All glass apparatus in use must be perfectly dry.)**

(2) The contents of the flask may be warmed gently over a water-bath so as to complete the formation of **sodium-ethoxide**.

(3) Allow the solution containing sodium ethoxide to cool to room temperature, add to it 5 g of *para*-acetylaminophenol, and then gradually introduce 4 ml of ethyliodide through the condenser, preferably in a dropwise manner.

(4) Heat the resulting reaction mixture under gentle reflux for a duration of 60–70 minutes, and then cool the contents in an ice-bath when phenacetin starts getting separated almost instantly.

(5) Filter it in a Büchner funnel under suction, wash the product with cold water and drain well.

4.1.2.4.9 Precautions :

(1) Sodium ethoxide should always be freshly prepared for their synthesis.

(2) Preferably the crude product produced in part–I *i.e.*, *para*-acetylaminophenol, must be recrystallized to obtain a pure crop of phenacetin in Part–II.

4.1.2.4.10 Recrystallization. In case, the product is not so pure, dissolve the whole of it in 40 ml of rectified spirit ; and add 1 g of powdered decolourizing carbon (*i.e.*, activated carbon), boil and filter. Treat the clear filtrate with 60 ml of hot water and allow to cool slowly in a refrigerator overnight. Collect the pure phenacetin on the Büchner funnel at the pump, squeeze out the excess of water with an inverted glass stopper, and dry in the air. The yield is 4.6 g (mp 136.5–137°C).

4.1.2.4.11 Theoretical yield/Practical yield. The theoretical yield is calculated from equation under section 4.1.2.4.6 (Part II) :

151.13 g of *p*-Acetylaminophenol upon interaction with 156 g of

Ethyliodide produces Phenacetin = 179.22 g

$\therefore$ 5 g of *p*-Acetylaminophenol shall yield Phenacetin $= \frac{179.22}{151.13} \times 5 = 5.929$ g

Hence, Theoretical yield of Phenacetin = **5.929 g**

Reported Practical yield = 4.6 g

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{4.6}{5.929} \times 100 =$ **77.5**

4.1.2.4.12 Physical Parameters. It is a slightly bitter, crystalline scales or powder. 1 g dissolves in 1300 ml cold water, 82 ml boiling water, 15 ml cold ethanol, 2.8 ml boiling ethanol, 14 ml chloroform, 90 ml ether, and soluble in glycerol. It gives a pasty mass with a salicylic acid, iodine, spirit nitrous ether, chloral hydrate, and phenol.

4.1.2.4.13 Uses

(1) It formed an integral component of **APC tablets**, also containing *aspirin* and *caffeine*. However, it has been withdrawn as a '*drug*' since early eighties by virtue of the fact that it may reasonably be anticipated to be **carcinogen**.*

(2) It possesses analgesic and antipyretic activities.

4.1.2.4.14 Questions for *Viva-Voce* :

(1) How is it that the active H-atom from the amino group in *p*-amino phenol gets preferentially abstracted as a mole of acetic acid rather than the H-atom of the —OH group ?

(2) Why should one use freshly prepared sodium ethoxide s a catalyst ?

(3) How does activated carbon particles help in decolourising/purifying a crude product ?

(4) Why do we get fine beautiful crystals from a slow-cooling process in comparison to rapid-cooling methods ?

4.1.2.4.15 Special Note :

(1) The pmr spectrum of pure crystalline **phenacetin** (DMSO-d_6, TMS) exhibits distinct signals at δ 1.30 (*t*, 3 H, Me), 2.0 (S, 3 H, COMe), 3.92 (*q*. 2 H, CH_2), 6.80 (*d*, 2 H, *ortho*-H's to OE *t*), 7.42 (*d*, 2 H, *ortho*-H's to NH) and 9.68 (*s* broad, 1 H, NH).

(2) In case, the mp is found to be **NOT** *satisfactory,* better cause dissolution of the product in dilute alkali in the cold and then reprecipitate it by the subsequent addition of an acid to the neutralization point. In fact, this procedure shall specifically erradicate traces of the **diacetate** of *p*-aminophenol that may be present. It is, however, pertinent to mention here that the acetyl group attached to the N-atom is not affected by cold dilute alkali, but the one attached to O-atom gets rapidly hydrolyzed by the reagent.

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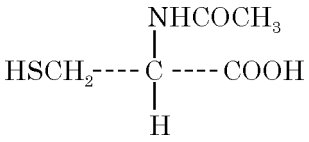
*Seventh Annual Report on Carcinogens (PB95-109781, 1994), p. 315.

4.1.2.5 Acetylcysteine :

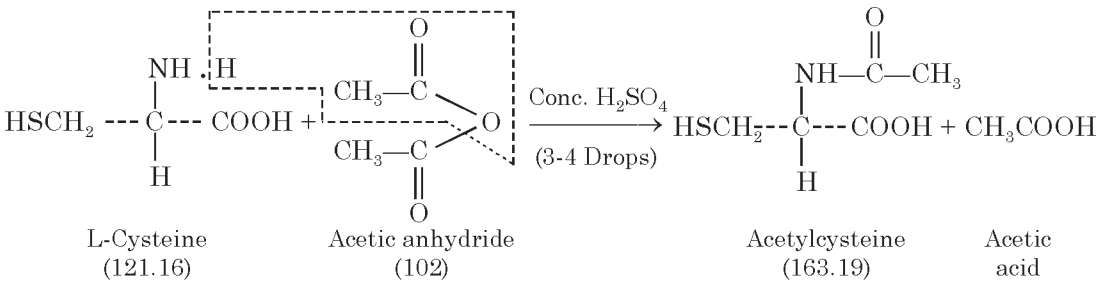
4.1.2.5.1 Chemical Structure :



Acetylcysteine

4.1.2.5.2 Synonyms. N-Acetyl-L-cysteine (NAC) ; L-Cysteine, N-acetyl- ; Mucomyst.

4.1.2.5.3 Theory



L-Cysteine is directly acetylated with acetic anhydride in the presence of a few drops of concentrated sulphuric acid to produce acetylcysteine and a mole of acetic acid. The H_2SO_4 present helps in the abstraction of one H-atom from the amino function of L-cysteine to form one mole of acetic acid as indicated above.

4.1.2.5.4 Chemicals Required. (1) L-Cysteine : 5.4 g ; (2) Acetic anhydride : 9.0 ml ; (3) Conc. Sulphuric acid : 3–4 drops.

4.1.2.5.5 Procedure. Follow the underlying steps sequentially :

(1) Weigh 5.4 of L-cysteine and transfer to a 100 ml conical flask.

(2) Add to the flask 9 ml of acetic anhydride and 3 to 4 drops of concentrated sulphuric acid carefully.

(3) Mix the contents of the flask intimately, and warm the mixture over a water-bath maintained at 60°C for about 20 minutes with intermittent stirring.

(4) Allow the contents of the flask to attain room temperature, and pour the contents in a thin stream right into 100 ml of cold water in a 250 ml beaker with frequent stirring with a glass rod.

(5) Filter the crude product on a Büchner funnel using suction, wash it generously with **cold water**, drain well and dry the product in an oven maintained at 80°C. The yield of crude acetylcysteine (mp 106–110°C) is approximately 5.9 g.

4.1.2.5.6 Precautions :

(1) All glass apparatus used in the above synthesis should be perfectly dry.

(2) Addition of 3–4 drops of concentrated sulphuric acid must be done very carefully.

(3) The reaction mixture is to be warmed at 60°C for a duration of 20 minutes only.

4.1.2.5.7 Recrystallization. The crude product may be recrystallized from a mixture of rectified spirit and water (1 : 1). The yield of pure white, crystalline powder (mp 106–109.5°C) is 5.75 g.

4.1.2.5.8 Theoretical yield/Practical yield. The theoretical yield is calculated from the equation under section 4.1.2.5.3 as given below :

121 g of L-Cysteine on reacting with 102 g of acetic anhydride

yields acetylcysteine = 163 g

$\therefore$ 5.4 g of L-cysteine shall yield acetylcysteine $= \frac{163}{121} \times 5.4 = 7.27$ g

Hence, Theoretical yield of Acetylcysteine = **7.27 g**

Actual Practical yield = 5.9 g

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{5.9}{7.27} \times 100 =$ **81.15**

4.1.2.5.9 Physical parameters. Acetylcysteine is a white, crystalline powder having a very slight acetic odour, and a specific characteristic sour taste. It is found to be fairly stable in ordinary light. It is nonhygroscopic in nature ; however, it gets oxidized in moist air. It is also stable at temperatures upto 120°C.It melts between 104–110°C. Its dissociation constant pK_a is 3.24. The pH of a 1 in 100 solution ranges between 2 to 2.75. It is soluble in water (1 g in 5 ml), ethanol (1 g in 4 ml), and almost insoluble in ether or chloroform.

4.1.2.5.10 Uses :

(1) It reduces the viscosity of pulmonary secretions and facilitate their removal.

(2) It is most effective in 10% to 20% solutions with a pH of 7 to 9 ; and is mostly employed either by **direct instillation*** or by **acerosol nebulization**.**

(3) Administration of N-Acetylcysteine (NAC) appears to reduce symptomatology associated with *influenza* and *influenza-like* episodes.

(4) Oral supplementation with NAC might be a prudent recommendation for smokers or individuals constantly exposed to second-hand smoke.

(5) NAC is the **antidote of choice** for acetaminophen (*i.e.*, paracetamol) overdose or poisoning.

(6) NAC seems to have some clinical usefulness as a **chelating agent** in the therapy of *heavy-metal poisoning.* (NAC effectively chelates Au, Ag and Hg.)

(7) NAC may have a beneficial therapeutic effect on ocular symptoms of **Sjogren's Syndrome**.***

***Instillation.** Slowly pouring or dropping a liquid into a cavity or onto a surface.

****Nebulization.** Production of particles such as a spray or mist from liquid.

*****Sjogren's Syndrome.** A chronic slowly progressive autoimmune disorder characterized by dryness of the eyes and mouth and recurrent salivary gland enlargement.

References :

(1) Wilson and Gisvold's : **Textbook of Organic Medicinal and Pharmaceutical Chemistry**, 10th edn., Delgado, J.N., and Remers, W.A., Lippincott-Raken, Publishers, New York, 1998.

(2) Gregory S. Kelly : **Clinical Applications of N-Acetylcysteine**, *Alt. Med. Rev.* **3** (2) : 114–127 (1998).

(3) De Vries N, and De Flora S : N-Acetyl-l-Cysteine, *J. Cell. Biochem* 17 F : S270–S277 (1993).

(8) NAC appears to have several possible therapeutic roles associated with heart disease, *viz*., it is found to enhance aspects of the effectiveness of nitroglycerine (NTG).

(9) It is also used as adjuvant therapy in *bronchopulmonary disorders,* when mucolysis is desirable.

(10) It also has been used with some success for the management of bowel obstruction due to **meconium ileus**, which is associated with newborn children with cystic fibrosis.

4.1.2.5.11 Questions for *Viva-Voce*

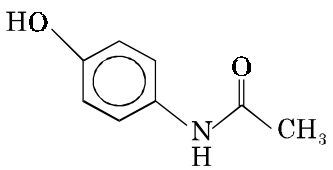
(1) Why is a 1% (*w*/*v*) solution of acetylcysteine highly acidic in nature (pH 2 to 2.75) ?

(2) Why is it absolutely necessary to carry out the reactions in perfect anhydrous conditions ?

(3) How would you explain the wide-spectrum of therapeutic efficacy of NAC–a very simple drug molecule ?

4.1.2.6 Paracetamol

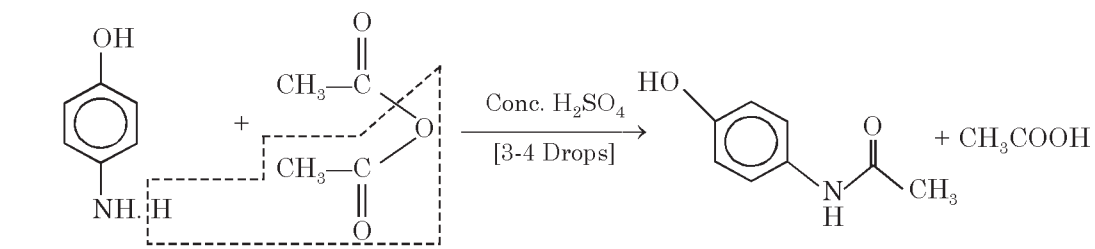
4.1.2.6.1 Chemical Structure



Paracetamol

4.1.2.6.2 Synonyms. Acetaminophen ; N-Acetyl-*p*-aminophenol ; N-(4-Hydroxyphenyl) acetamide ; Calpol ; Tylenol ; Panadol ; Disprol ; Parmol ; Valdol ; Pacemol ; Naprinol.

4.1.2.6.3 Theory



para-Aminophenol (109.13) | Acetic anhydride (102) | Paracetamol (151.17) | Acetic acid

Many preparative methods have since been described for the synthesis of paracetamol, mostly employing the acetylation of *para*-aminophenol with acetic anhydride as indicated above. However, a number of *other routes of synthesis* have also been discovered and used commercially, namely :

(*a*) **Phenol—**is converted to *para*-nitrosophenol and then reduced and acetylated,

(*b*) **Late sixties—**a single-step synthesis from **nitrobenzene** to *para*-aminophenol was *patented*,

(*c*) **Late seventies—**observed a new entrant to the field using a process starting from **monochlorobenezene** followed by *nitration, hydrolysis* and *acetylation*,

(*d*) **Mid-eighties—**saw an altogether '*new route of synthesis*' starting from **phenol**, but employing an **innovative technology** *via* **4-hydroxyacetophenone** followed by a *rearrangement* to **paracetamol**, and

(*e*) **Paracetamol—**synthesis by one-step *Pd-La/C catalytic hydrogenation* and *acylation**. Here, *para*-nitrophenol is used as a starting material. The optimal reaction conditions are as follows : reaction temperature 140°C, reaction pressure 0.7 MPa and reaction time 2 hours. The yield of paracetamol is upto 97%.

4.1.2.6.4 Chemicals Required. *para*-Aminophenol : 6 g ; Acetic anhydride : 6.5 ml ; Concentrated Sulphuric acid : 4 drops.

4.1.2.6.5 Procedure. The various steps are enumerated as under :

(1) Weigh 6 g of *para*-aminophenol and transfer to a 100 ml thoroughly cleaned and dried conical flask.

(2) Add to the flask 6.5 ml of acetic anhydride and 3–4 drops of concentrated sulphuric acid **cautiously**.

(3) The contents of the flask may be mixed thoroughly. Warm the mixture on a water-bath previously maintained at 60°C for about 20–25 minutes with constant stirring.

(4) Allow the contents of the flask to attain room temperature, and pour it directly into a beaker having 100 ml of cold water (with a few chips of crushed ice) and stir it vigorously.

(5) The crude product obtained in (4) is filtered onto a Büchner funnel using suction, wash it with plenty of **cold water**, drain well and dry the product either between the folds of filter paper and air-dry it or dry it in an electric oven maintained at 100°C. The yield of crude paracetamol (169–170.5°C) is approximately 6.8 g.

4.1.2.6.6 Precautions

(1) All glass apparatus which are used in the synthesis must be perfectly dry.

(2) Concentrated sulphuric acid should always be added with great caution.

(3) To complete the reaction mixture it must be warmed at 60°C for 20–25 minutes.

4.1.2.6.7 Recrystallisation. Dissolve the crude product in 70% (*v*/*v*) ethanol and warm it to 60°C ; add 2 g of powdered animal charcoal (decolourizing carbon). Filter and concentrate the filtrate over a water-bath. Allow it to cool and large monoclinic crystals will separate out. The yield of the pure paracetamol (mp 169–170.5°C) is 6.5 g.

4.1.2.6.8 Theoretical yield/Practical yield

109 g of *p*-Aminophenol on acetylation with 102 g of acetic anhydride yields Paracetamol = 151 g

6 g of *p*-Aminophenol shall yield Paracetamol $= \frac{151}{109} \times 6 = 8.31$ g

Hence, Theoretical yield of Paracetamol = **8.31 g**

*Fang Yanxiong *et al., 'Modern Chemical Industry'* , July, 2000.

Reported Practical yield = 6.8 g

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{6.8}{8.31} \times 100 = \mathbf{81.82}$

4.1.2.6.9 Physical Parameters. Paracetamol is obtained as large monoclinic prisms obtained from water having mp 169–170.5°C, and has a slightly bitter taste. It shows d_1^{21} 1.293 ; uv_{max} (ethanol) : 250 nm ($\in$ 13800). It is found to be very slightly soluble in cold water and considerably more soluble in hot water ; soluble in methanol, ethanol, DMF, ethylene dichloride, acetone, ethyl acetate ; slightly soluble in ether ; and almost insoluble in petroleum ether, pentane and benzene.

4.1.2.6.10 Uses

(1) It is an effective *antipyretic* and *analgesic* ; the former activity *i.e.*, **antipyresis** is caused by acting on the hypothalamic heat-regulating centre, whereas the latter action *i.e.*, **analgesia** by elevating the pain-threshold.

(2) It is also found to be useful in diseases accompanied by pain, discomfort, and fever, for instance : the common cold and other viral infections.

(3) It is also effective in a wide spectrum of *arthritic* and *rheumatic* conditions involving *musculoskeletal pain* as well as the pain caused due to headache, dysmenorrhea*, myalgias,** and neuralgias.***

(4) Unlike aspirin, paracetamol **does not antagonize** the effects of *uricosuric agents*.

4.1.2.6.11 Questions for *Viva-Voce*

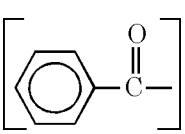
(1) Is it possible to prepare '*Paracetamol*' from *para*-Nitrophenol ?

(2) What is the latest mode of synthesis for '*Paracetamol*' by Pd-La/C catalytic hydrogenation and acylation of *p*-Nitrophenol ?

(3) What physico-chemical analytical technique would you use to check its purity ?

4.2 BENZOYLATION METHODS

4.2.1 Introduction

The insertion of a benzoyl moiety  instead of the active hydrogen atom present in hydroxyl (—OH), primary amino ($—NH_2$) or secondary amine function (> NH) is usually termed as the '**Benzoylation Reaction**'. Interestingly, this particular reaction essentially bears a close resemblance to the phenomenon of '*Acetylation*', except that in this specific

*__Dysmenorrhea :__ Pain in association with menstruation.

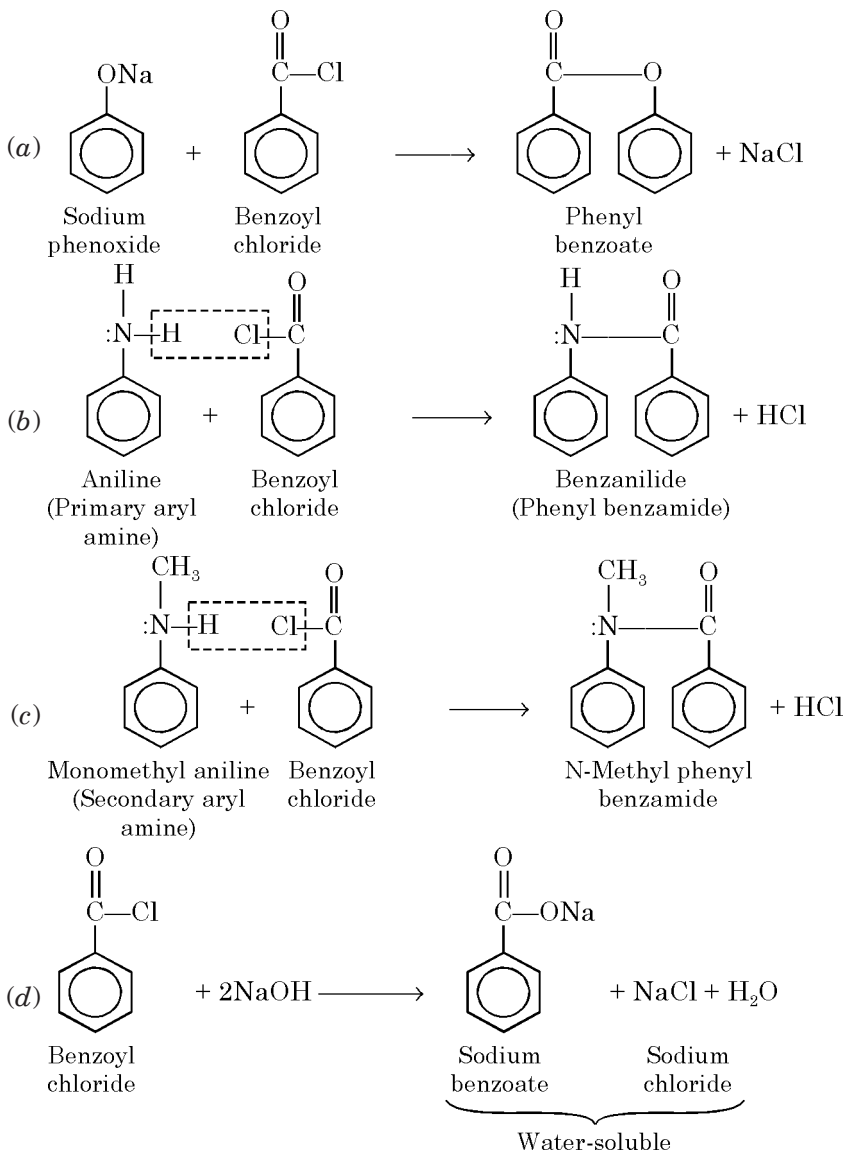
**__Myalgias :__ Tenderness or pain in the muscles.

***__Neuralgias :__ Severe sharp pain occurring along the course of a nerve.

instance the reagent employed is '**benzoyl chloride**' which reacts in the presence of **Pyridine** or *Sodium hydroxide* and NOT benzoic anhydride (as in the case of '*acetylation*').

Schotten-Baumann Reaction. In the Schotten-Baumann method of benzoylation, the hydroxyl or amino compound (or a salt of the latter) is either suspended or dissolved in an excess of freshly prepared *10%* (*w/v*) *aqueous sodium hydroxide solution*, together with a *small excess of benzoyl chloride* (*i.e.*, nearly 10% more than the theoretical quantity), and the resulting mixture is shaken vigorously in ambient conditions. It has been observed that under these experimental parameters '**benzoylation**' proceeds smoothly. Thus, the solid benzoylated product, which being insoluble in the aqueous medium, gets separated briskly. Simultaneously, the NaOH solution hydrolyses the excess of benzoyl chloride present in reaction mixture, thereby resulting into the formation of **sodium chloride** and **sodium benzoate**, which being water-soluble remain in solution.

The various reactions that are involved in the **Schotten-Baumann method of benzoylation** are as given below :



Explanation

Equation (*a*) Phenol first undergoes dissolution in sodium hydroxide solution to result into the formation of *sodium phenoxide*, which on being subjected to benzoylation yields **phenyl benzoate**.

Equation (*b*) Likewise, aniline *i.e.,* a primary aryl amine, gives rise to the formation of **benzanilide** or *phenyl benzamide* or *benzoyl aniline* as the final product plus one mole of HCl.

Equation (*c*) Monomethyl aniline *i.e.,* a secondary aryl amine, undergoes benzoylation to produce **N-methyl phenyl benzamide** or benzoyl monomethylaniline plus one mole of HCl.

Equation (*d*) Excess of benzoyl chloride in the reaction mixture is hydrolysed by sodium hydroxide thereby resulting into the formation of **sodium benzoate** and **sodium chloride**, which being water soluble remain in the solution whereas the corresponding benzoylated product (insoluble) may be separated conveniently.

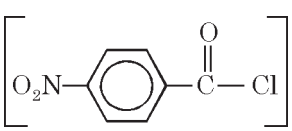
Advantages of Benzoylation over Acetylation. There are, in fact, *two* major advantages of benzoylation over acetylation, namely :

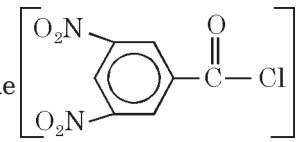
(*a*) *First*, generally the benzoyl derivatives are obtained as crystalline solids having comparatively **higher melting points** than the corresponding acetyl derivatives ; besides, possessing **lower solubilities** in a wide range of solvents, and

(*b*) *Secondly*, the benzoyl derivatives may be prepared rapidly and conveniently in **aqueous medium**, as compared to the 'acetylation' carried out in acetic anhydride, acetyl chloride, and glacial acetic acid ; in addition to the fact that *benzoyl chloride* undergoes hydrolysis rather extremely slowly and sluggishly.

Precautionary Measures. There are *two* cardinal precautionary measures that have to be taken into consideration while carrying out *Schotten-Baumann benzoylation method*, such as :

(1) It has been observed that the '*benzoylated products*' when get separated during the course of Schotten-Baumann reaction, they invariably occlude tracess of unreacted benzoyl chloride from the reaction mixture, which eventually escapes hydrolysis by the alkali (NaOH) in the reaction medium. Therefore, it is not only an **absolute necessity** but also **advantageous** to recrystallize the benzoylated products either from *ethanol* or *methylated spirit* so as to enable these '*solvents*' to esterify the unchanged benzoyl chloride and allow them subsequently to be removed from the final recrystallized benzoylated material, and

(2) Occasionally, it has been noticed that *benzoyl chloride* results into a product that does not yield definite final crystallized material. The ensuing difficulty arising from such specific instances may be overcome by making use of **alternative benzoylating reagents**, namely : *para*-nitrobenzoyl chloride  or 3, 5-

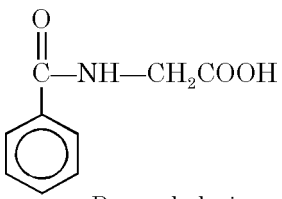
dinitrobenzoyl chloride  , which normally produce definite and specific **crystalline derivatives**.

4.2.2 Syntheses of Medicinal Compounds

A few typical medicinal compounds that are prepared by the aforesaid benzoylation methods shall be discussed explicitely in the sections that follow, namely : Benzoyl Glycine ; N-Benzoyl-β-Alanine ; Flavone ; Benzoyl Peroxide ; Benzyl benzoate.

4.2.2.1 Benzoyl Glycine

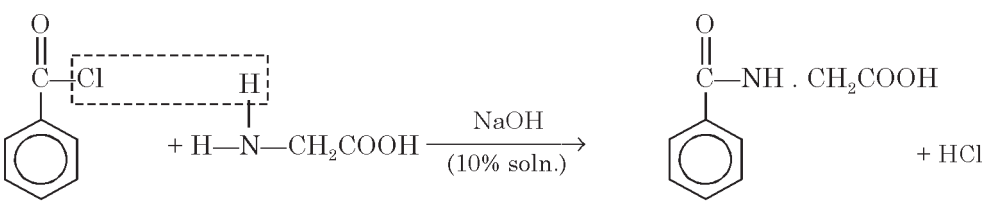
4.2.2.1.1 Chemical Structure



Benzoyl glycine

4.2.2.1.2 Synonyms. Hippuric Acid ; Benzoylaminoacetic acid ; Benzamido-acetic acid.

4.2.2.1.3 Theory



Benzoyl chloride (135.5) Glycine (75.07) Benzoyl glycine (179.18)

Glycine (*i.e.,* α-aminoacetic acid) interacts with one mole of benzoyl chloride, in the presence of 10% (*w/v*) NaOH solution, to yield benzoyl glycine with the elimination of one mole of HCl. The excess of 10% NaOH solution serves two purposes, namely : *first*, to remove the unreacted benzoyl chloride as explained under section 4.2.1 Eq. (*d*) ; and *secondly*, the HCl eliminated reacts with NaOH to yield NaCl. Interestingly, both sodium benzoate and sodium chloride are water-soluble, whereas the desired product benzoyl glycine being insoluble may be separated easily.

4.2.2.1.4 Chemicals Required. Glycine 5 g ; Sodium hydroxide solution 10% (*w/v*) : 50 ml ; Benzoyl chloride : 10.8 g (9.0 ml) ; Carbon tetrachloride : 20 ml ; Conc. Hydrochloric acid : 5 ml ;

4.2.2.1.5 Procedure. The various steps involved are as follows :

(1) Dissolve 5 g (0.33 mol) of glycine in 50 ml of 10% NaOH solution contained in a 250 ml conical flask.

(2) Transfer 10.8 g (9 ml, 0.385 mol) of benzoyl chloride in approximately five equal lots to the above solution (1).

(3) Stopper the 250 ml flask securedly with a rubber-cork and shake the contents vigorously after each addition unless and until all the benzoyl chloride has virtually reacted.

(4) Pour the contents of the flask to a 250 ml beaker and rinse the flask with a little water.

(5) Add a few grams of crushed-ice into the solution and acidify the contents by adding concentrated hydrochloric acid dropwise and carefully with constant stirring until the mixture is acid to Congo red paper (pH 5.0 Red ; pH 3.0 Blue-Violet).

(6) Collect the resulting crystalline precipitate of benzoyl glycine, which is contaminated with a small amount of benzoic acid, on a Büchner funnel, wash with cold water and drain well by the help of an inverted glass stopper.

(7) Transfer the solid into a beaker containing 20 ml of carbon tetrachloride, cover it with a clean water-glass, and boil it gently over an electric water-bath for 10 minutes (bp CCl_4 76.7°C). Thus, it will extract any benzoic acid which may have been produced during the course of reaction (FUME CUPBOARD).

(8) The resulting mixture is allowed to cool slightly, filter under gentle suction and wash the crude product on the filter with 10-20 ml of CCl_4. The yield of the crude benzoyl glycine (mp 185–186.5°C) is 9.2 g.

4.2.2.1.6 Precautions

(1) The addition of benzoyl chloride to the alkaline mixture of glycine must be carried out slowly and that too under different stages.

(2) Continuous shaking of the above mixture be done till the whole of benzoyl chloride has reacted.

(3) It is necessary to render the resulting mixture to acidic conditions with Congo Red paper.

4.2.2.1.7 Recrystallization. Recrystallize the dried crude product from 100 ml of boiling distilled water with the addition of 1–2 g of powdered decolourizing carbon (activated carbon), if necessary, filter through a hot-water funnel and allow to crystallize. Collect the benzoyl glycine on a Büchner funnel under suction and dry the pure product in an oven maintained at 110°C. The yield is 8.8 g (mp 186.5-187°C).

4.2.2.1.8 Theoretical yield/Practical yield. The theoretical yield is calculated from the equation under theory (section 4.2.2.1.3) as given below :

75.07 g of Glycine on reaction with 135.5 g of Benzoyl chloride

yields Benzoyl glycine = 179.18 g

$\therefore$ 5 g of Glycine shall yield Benzoyl glycine $= \frac{179.18}{75.07} \times 5 = 11.9$ g

Hence, Theoretical yield of Benzoyl glycine = **11.9 g**

Reported Practical yield = 8.8 g

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{8.8}{11.9} \times 100 = \mathbf{73.9}$

4.2.2.1.9 Physical Parameters. It is obtained as crystals having mp 187–188°C. It is freely soluble in hot ethanol, hot water, and also soluble in aqueous solution of sodium phosphate.

4.2.2.1.10 Uses. Conjugation with amino acids is an important route in the conjugation of drug and xenobiotic carboxylic acids for elimination.*

These amino acid conjugates are usually less toxic than their precursor acids and hence, are excreted readily into the urine and bile.

4.2.2.1.11. Questions for *Viva-Voce*

(1) What are the two specific roles played by excess of 10% NaOH solution ?

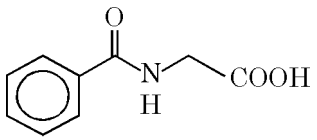
(2) How does a small quantity of *benzoic acid* formed along with benzoyl glycine ?

(3) Why is it necessary to acidify the reaction mixture in the presence of *crushed-ice* with conc. HCl ?

(4) How does activated carbon help in removing the dirty colour of the product during the process of recrystallization ?

4.2.2.2 N-Benzoyl-β-Alanine

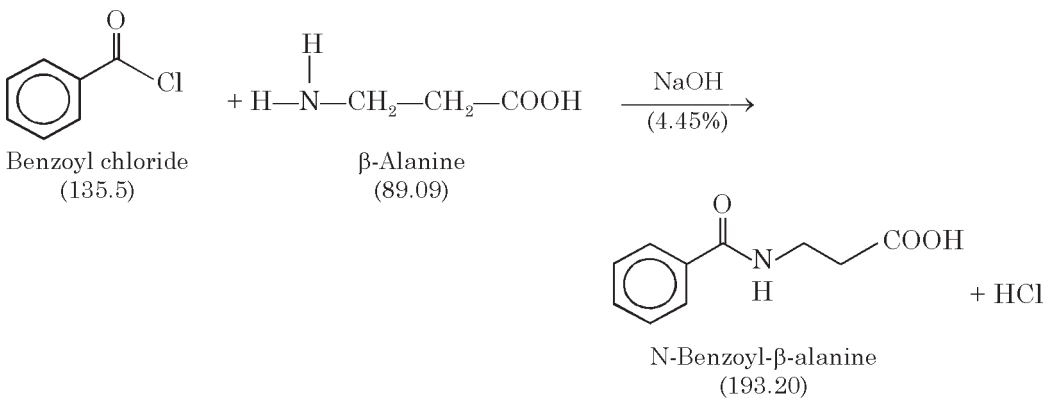
4.2.2.2.1 Chemical Structure



N-benzoyl-β-alanine

4.2.2.2.2 Synonyms. Betamipron ; 3-(Benzoylamino)-propionic acid ; β-Benzamidopropionic acid.

4.2.2.2.3 Theory



Benzoyl chloride (135.5)

β-Alanine (89.09)

N-Benzoyl-β-alanine (193.20)

*Mulder G.J., Ed., *Conjugation reactions in drug metabolism : An integrated approach*, Taylor and Francis, New York, 1990.

β-Alanine interacts with benzoyl chloride in the presence of sodium hydroxide solution to yield N-benzoyl-β-alanine with the elimination of one mole of HCl. The excess of unreacted benzoyl chloride is converted to soluble sodium benzoate with the help of NaOH ; and the liberated HCl gets reacted with NaOH to yield water soluble NaCl. The resulting desired product is insoluble in ice-cold water.

4.2.2.2.4 Chemicals Required. β-Alanine : 10 g ; Benzoyl Chloride : 17.5 g ; Sodium Hydroxide : 9.5 g ; Decolourizing Charcoal : 1.0 g ; Conc. HCl : 5 ml.

4.2.2.2.5 Procedure. The various steps involved are as follows :

(1) Dissolve 10 g (1.1 mol) of β-alanine in 40 ml of water containing 4.45 g (1.1 mol) of sodium hydroxide ; and cool the resulting solution in an ice-bath.

(2) Add 17.5 g (1.2 mol) of benzoyl chloride and a solution of 4.9 g (1.2 mol) of NaOH in 20 ml of water into the previously chilled amino acid solution with constant stirring into small lots at intervals over a period of 2 hours. Continue the stirring for a further duration of 2 hours so as to complete the reaction.

(3) Boil the resulting mixture with 1 g of decolourizing charcoal for 15-20 minutes, filter the crude product in a Büchner funnel fitted with a air-suction device ; and cool the clear yellowish filtrate to 0°C in a freezing-mixture.

(4) Carefully acidify the chilled filtrate to Congo Red with concentrated HCl dropwise.

(5) Triturate a portion of the oil that separates with water to induce the process of crystallization. Subsequently, the bulk of the acidified solution is seeded with crystals and allow it to cool in an ice-bath for several hours so as to complete the crystallization process.

(6) Filter off the crude product, wash the filter-cake with about 60 ml of chilled water. The yield of crude N-benzoyl-β-alanine (mp 131–133°C) is approximately 20.2 g.

4.2.2.2.6 Precautions

(1) The addition of benzoyl chloride and NaOH solution to the amino-acid solution must be accomplished very slowly with constant stirring over a period of 2 hours, otherwise the reaction may not be completed *i.e.,* benzoylation shall not be fully achieved.

(2) Acidification of the filtrate with conc. HCl must be done in chilled condition to avoid any possible deterioration of the final product.

4.2.2.2.7 Recrystallization. Recrystallize 20 g of the crude product from 350 ml of boiling water. About 1 g of decolourising charcoal may be added, if the solution has a pale-yellowish colouration. The yield of pure N-benzoyl-β-alanine (mp 132-132.5°C) is 18.2 g.

4.2.2.2.8 Theoretical yield/Practical yield. The theoretical yield is calculated from the equation under theory (section 4.2.2.2.3) as given below :

89.09 g of β-Alanine on treatment with 135.5 g of Benzoyl

Chloride yields N-Benzoyl-β-Alanine = 193.20 g

$\therefore$ 10 g of β-Alanine shall yield N-Benzoyl-β-Alanine $= \frac{193.2}{89.09} \times 10 = 21.68$ g

$\therefore$ Theoretical yield of N-Benzoyl-β-Alanine **= 21.68 g**

Reported Practical yield = 20.2 g

Therefore, Percentage Practical yield $= \frac{20.2}{21.68} \times 100 =$ **93.17**

4.2.2.2.9. Physical Parameters. It is obtained as colourless prisms from hot water having mp 132.5–133°C. It is found to be readily soluble in warm water and chloroform ; and very easily soluble in alcohol, ether and acetone.

4.2.2.2.10. Uses

(1) It is mostly used as an antibacterial adjunct

(2) It is invariably employed as a nephroprotective agent *i.e.*, acts as a renal protectant.

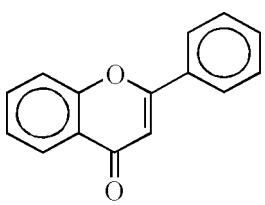
4.2.2.2.11. Questions for *Viva-Voce*

(1) Why is it necessary to add a few seeds of pure crystals to initiate crystallization ?

(2) Why is it important to add benzoyl chloride and NaOH solution very slowly to the amino-acid solution ?

4.2.2.3 Flavone

4.2.2.3.1 Chemical Structure :



Flavone

4.2.2.3.2 Synonyms. 2-Phenyl Chromone ; 2-Phenyl-γ-benzopyrone ; 2-Phenyl-1, 4-benzopyrone.

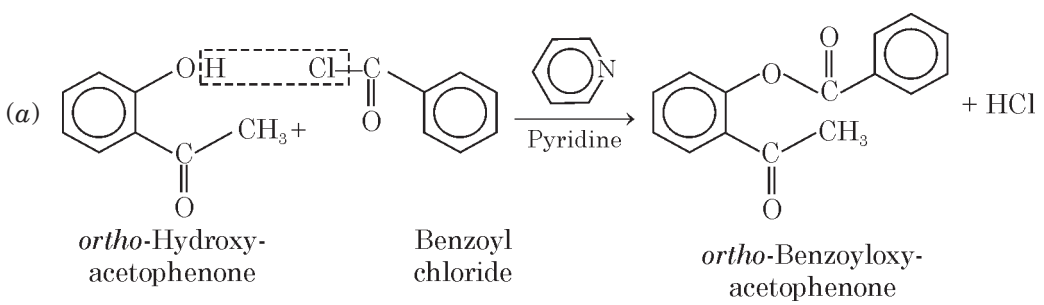
There are *two* methods for the preparation of **'flavone'**, namely :

(*i*) From *ortho*-benzoyloxyacetophenone and conversion of it into *flavone* by heating with pure redistilled glycerol (**2-Step Synthesis**),

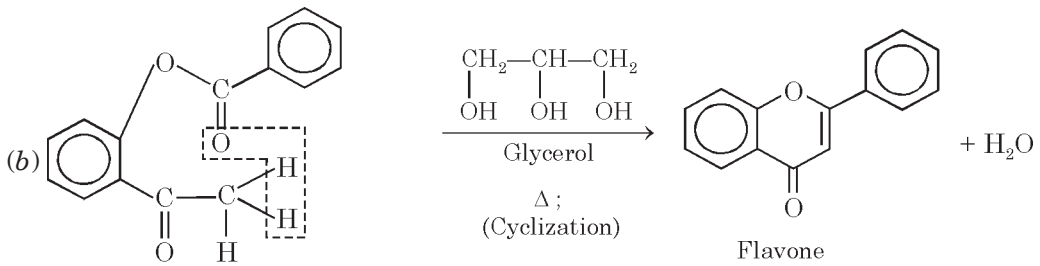
(*ii*) From *ortho*-benzoyloxyacetophenone, conversion to *ortho*-hydroxybenzoylmethane, and finally to *flavone* by treatment with sylphuric acid (**3-Step Synthesis**).

However, the relatively simpler two-step synthesis for **FLAVONE** shall be discussed in the sections that follow :

4.2.2.3.3 Theory

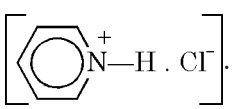


ortho-Hydroxy-acetophenone — Benzoyl chloride — *ortho*-Benzoyloxy-acetophenone



ortho-Benzoyloxy-acetophenone (240)

Flavone (222.24)

Equation (*a*) *o*-Hydroxyacetophenone on benzoylation with benzoyl chloride in the presence of basic medium due to the presence of pyridine gives rise to the formation of *o*-benzoyloxy-acetophenone, and a mole of hydrochloric acid is liberated. The liberated HCl instantly combines with the pyridine (basic) present in the medium to yield the corresponding salt pyridinium chloride  .

Equation (*b*) The *o*-benzoyloxyacetophenone on heating and treatment with freshly distilled anhydrous glycerol, in an absolute inert atmosphere, abstracts a mole of water ; and ultimately undergoes *cyclization* to yield **flavone**.

4.2.2.3.4 Chemicals Required. For Step I. *o*-Hydroxyacetophenone : 6.8 g (6 ml ; 0.1 mole) ; Benzoyl chloride : 10.55 g (8.7 ml ; 0.15 mole) ; Pyridine : 10 ml ; Hydrochloric acid [3% (*v*/*v*)] : 300 ml ; Crushed ice : 100 g ; Methanol : 25 ml.

For Step II. *o*-Benzoyloxyacetophenone : 8 g (0.083 mole) ; Glycerol (anhydrous freshly distilled) : 80 ml ; Ligroin (bp 60–70°C) or Acetone (bp 56.5°C) : 160 ml.

4.2.2.3.5 Procedure. The *two* steps are described separately as below :

Step I. *ortho*-Benzoyloxyacetophenone

(1) Take a 100 ml conical flask, fitted with a **Calcium-chloride Drying Tube** and transfer into it 6.8 g (6 ml ; 0.1 mole) of *ortho*-hydroxyacetophenone, 10.55 g (8.7 ml ; 0.15 mole) of benzoyl chloride, and 10 ml of redistilled pyridine.

(2) It is pertinent to mention here that the **temperature** of the reaction mixture **rises almost instantaneously**.

(3) After a gap of about 15–20 minutes when no further heat appears to evolve, the resulting reaction mixture is poured in the form of a thin stream into a beaker containing 300 ml of (3%) HCl and 100 g of crushed ice along with **constant and vigorous stirring**.

(4) The crude product separates out which is subsequently collected on a Büchner funnel, washed with 10 ml of methanol, followed by 10 ml of water. The product is squeezed thoroughly with the help of an inverted glass-stopper while the suction is still on. It is finally dried at room temperature.

The yield of the crude dry product (mp 81.5–86.5°C) is approximately 10–10.5 g.

Precautions

(1) The pyridine (Laboratory Grade) should be adequately dried over solid sodium hydroxide flakes or granules and distilled through a fractionating column and fractions collected between 115.2–115.3°C.

(2) The first two stages *i.e.,* (1) and (2) of *Step I* must be carried out under perfect anhydrous conditions so that the main reaction takes place almost perfectly and completely.

(3) Allow the reaction mixture to stand, after the vigorous and instant exothermic reaction, for the stipulated duration so as to complete the reaction.

Recrystallization. The crude product is recrystallized from 15 ml of methanol, and the pure white crystals of *ortho*-benzoyloxyacetophenone (mp 76.5–77.5°C) is obtained between 9–9.5 g.

Step II. Flavone

(1) Set up a 250 ml round-bottomed 3-necked flask adequately equipped with a Hg-sealed variable-speed mechanical stirrer, a thermometer, and an air-condenser closed with a $CaCl_2$-drying tube in the *second-neck*, are transferred 8 g (0.083 mole) of recrystallized and dried *o*-benzoyloxyacetophenone and 80 ml of **freshly distilled anhydrous glycerol**.

(2) Through the *third-neck* introduce a fine-stream of NITROGEN gas, dried **on-line** by passing through a wash bottle filled with sulphuric acid ($d \sim 1.84$).

(3) The resulting mixture is heated and maintained at 260°C over an electric heating mantle for a duration of 2 hours while being stirred continuously with the aid of a mechanical stirrer.

(4) The contents of the reaction flask are cooled below 90°C, and then poured in one-go directly into a 2 L beaker containing water which has been previously made alkaline by the addition of sodium hydroxide solution (0.1 M).

(5) The mixture is thoroughly stirred for 20 minutes, cooled and kept at 0°C for 48 hours in a refrigerator, when tan-coloured crystals of **flavone** are obtained.

(6) Filter the crude tan-coloured crystals on a Büchner funnel under suction and dry at 50°C. The yield of the product (mp 96–96.5°C) is between 3.2 to 3.4 g.

Precautions

(1) The glycerol to be used in this synthesis **must** be double-distilled under reduced pressure (vacuum) and to be used immediately in the reaction.

(2) The reaction proceeds in an absolute anhydrous condition and that too in an **inert** atmosphere of nitrogen gas.

(3) The appearance of crystals of flavone takes place only after thorough chilling and storage at 0°C for 2 days.

Recrystallization. The crude product is dissolved in 160 ml of hot ligroin or acetone. Subsequently, repeated partial evaporation of the solvent in several stages, each followed by chilling, yields successive crops of flavone as white needles. The yield of pure flavone (mp 99–100°C) is 2.8 to 3.0 g.

4.2.2.3.6 Theoretical yield/Practical yield. The theoretical yield of flavone may be calculated from equation (*b*) under theory (section 4.2.2.3.3) as mentioned below :

240 g of *o*-Benzoyloxyacetophenone yields Flavone = 222.24 g

$\therefore$ 8 g of *o*-Benzoyloxyacetophenone shall yield Flavone $= \frac{222.24}{240} \times 8 = 7.40$ g

Hence, Theoretical yield of Flavone = **7.40 g**

Reported Practical yield of Flavone = 2.8 g

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{2.8}{7.4} \times 100 =$ **37.83.**

4.2.2.3.7 Physical Parameters. Flavone is obtained as crystals from petroleum ether having mp 99–100°C. It is found to be practically insoluble in water, but soluble in most organic solvents. Pure crystalline flavone exhibits absorption maxima at 350 and 405 nm.

4.2.2.3.8 Uses. Indeed, there is a growing belief that certain flavonoids and flavones are specifically useful, acting as antioxidants and giving protection against cardiovascular disease, certain forms of cancer, and, it is also claimed, age-related degeneration of cell components.

4.2.2.3.9 Questions for *Viva-Voce*

(1) Why pyridine is added to the benzoylation process of *ortho*-hydroxyacetophenone ?

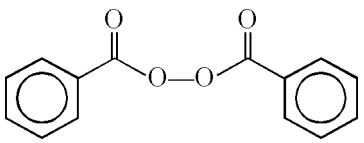
(2) What will happen to the liberated HCl in the above reaction ?

(3) Why is it absolutely necessary to make use of freshly prepared double-distilled glycerine in the '*cyclization*' of *ortho*-benzoyloxyacetophenone ?

(4) The above reaction involving cyclization must be carried out in an '*inert atmosphere*'. Explain ?

4.2.2.4 Benzoyl Peroxide

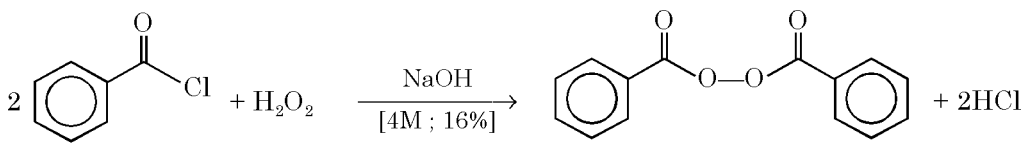
4.2.2.4.1 Chemical Structure



Benzoyl peroxide

4.2.2.4.2 Synonyms. Dibenzoyl peroxide ; Benzoyl superoxide.

4.2.2.4.3 Theory



Benzoyl chloride (135.5) — Hydrogen peroxide (34) — Benzoyl peroxide (242.23)

Benzoyl chloride interacts with hydrogen peroxide in the presence of sodium hydroxide solution to give rise to benzoyl peroxide with the elimination of two moles of hydrochloric acid. The above reaction, being '*exothermic*' in nature, should be carried out in an ice-bath. The excess of sodium hydroxide present in the reaction mixture converts the unreacted benzoyl chloride into sodium benzoate ; and also reacts with liberated HCl to give sodium chloride. Thus, both sodium benzoate and NaCl being water-soluble remain in the solution, whereas the *sparingly soluble* benzoyl peroxide gets separated in the reaction mixture.

4.2.2.4.4 Chemicals Required. Benzoyl Chloride (redistilled) : 30 g (25 ml) ; Sodium Hydroxide solution [16% (*w/v*) ≡ 4 M.NaOH] : 30 ml ; Hydrogen Peroxide [12% (40 Volume)] : 50 ml.

4.2.2.4.5 Procedure. The various steps involved are stated below in a sequential manner :

(1) Place a 500 ml beaker in an ice-bath in a *Fume-Cupboard*, and transfer 50 ml (0.175 mole) of hydrogen peroxide into it. Equip the beaker with a variable-speed mechanical stirrer.

(2) Arrange to support two 100 ml dropping funnels, containing respectively 30 ml of NaOH solution and 25 ml (30 g) of freshly redistilled benzoyl chloride (**Lachrymatory**), having their stems positioned reasonably inside the beaker.

(3) Continue adding the **two** reagents *i.e., benzoyl chloride* and *sodium hydroxide solution*, into the beaker dropwise at a time **Alternately**, taking special care that the pH of the reaction mixture is always maintained **faintly alkaline** ; and **Most Importantly** the temperature of the reaction mixture must not rise above 5–8°C.

(4) When the addition of all the reagents have accomplished, continue stirring the reaction mixture for a further duration of 30-40 minutes ; and observe that by now the characteristic pungent odour of benzoyl chloride must have been subsided considerably.

(5) Filter off the flocculent white precipitate on the Büchner funnel under suction, wash it with a small quantity of cold water, and subsequently air-dry upon filter paper.

The yield of crude benzoyl peroxide* is approximately 11.2 g having mp 101-102.5°C.

4.2.2.4.6. Precautions

(1) Always use freshly redistilled benzoyl chloride so as to accomplish better yield and also a better product.

(2) The benzoylation reaction **must** be carried in an ice-bath and at no stage the temperature of the reaction mixture be allowed to go beyond 5–8°C.

(3) Further vigorous stirring of the reaction mixture, after complete addition of benzoyl chloride and NaOH solution, is absolutely essential so as to **Complete** the reaction process.

(4) **Do not dry the Crude Product in an oven as Benzoyl Peroxide may explode on Heating.**

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*Alternatively, **BENZOYL PEROXIDE**, may also be prepared by interaction of benzoyl chloride and a cooled solution of sodium peroxide [A.I. Vogel, *Practical Organic Chemistry*, Longmans, London, 3rd ed., (1954)].

4.2.2.4.7 Recrystallization. Recrystallize the crude product by dissolving in chloroform strictly at **Room Temperature only** and adding twice the volume of **absolute methanol**.

[Note. Benzoyl peroxide must Not be recrystallized from Hot chloroform, because a Serious Explosion may take place.]

The yield of the pure recrystallized product is 10.6 g with mp 105–106°C.

Special Precautionary Note. Just like other Organic Peroxides, benzoyl peroxide may be handled with utmost care and restrain behind well-guarded shatter-proof screens ; and always horn or moulded polyethylene (Not Nickel or Stainless Steel) spatulas must be employed. It is an extremely Shock-Sensitive substance.

4.2.2.4.8 Theoretical yield/Practical yield. The theoretical yield is calculated from the equation given under theory (Section 4.2.2.4.3) as given below :

271 g of Benzoyl Chloride (2 moles) when reacts with 34 g of

H_2O_2 yields Benzoyl Peroxide = 242.23 g

$\therefore$ 30 g of Benzoyl Chloride should yield Benzoyl Peroxide $= \frac{242.23}{271} \times 30 = 26.8$ g

Hence, Theoretical yield of Benzoyl Peroxide = **26.8 g**

Reported Practical yield = 10.60 g

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{10.6}{26.8} \times 100 =$ **39.5**

4.2.2.4.9 Physical Parameters. It is obtained as crystals or white granular powder having mp 103-106°C. **It may explode when heated**. It is found to be sparingly soluble in water or ethanol ; soluble in benzene, chloroform, and ether. 1 g Dissolves in 40 ml of carbon disulphide (CS_2), and in nearly 50 ml of olive oil. It has a characteristic odour.

4.2.2.4.10 Uses

(1) It possesses **mild antibacterial** properties, especially against anaerobic bacteria.

(2) It exerts moderate *keratolytic** and *antiseborrheic*** actions.

(3) It is mainly used in the treatment of mild *acne vulgaris* (in which it is comedolytic***) and *acne rosacea*.

(4) It is also employed in the treatment of *decubital***** and *statis ulcers*.*****

4.2.2.4.11. Questions for *Viva-Voce*

(1) Why is it required to carry out the benzoylation reaction in an ice-bath ?

(2) Why is it necessary to add benzoyl chloride and NaOH solution into the peroxide alternately in a faintly alkaline medium ?

---

*__Keratolytic.__ Causing loosening of the horny layer of the skin.

**__Antiseborrheic.__ An agent that relieves seborrhea (*i.e.,* an oil-secreting gland of the skin).

***__Comedolytic.__ The typical small skin lesion of *acne vulgaris*.

****__Decubital.__ A bedsore.

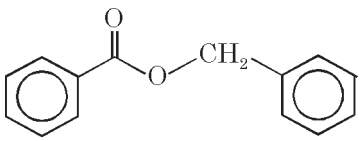
*****__Statis ulcers.__ An open lesion of the skin.

(3) Why does the crude product not dried in an oven ?

(4) Why is it necessary to recrystallize the crude product from chloroform particularly at room temperature only ?

4.2.2.5. Benzyl Benzoate

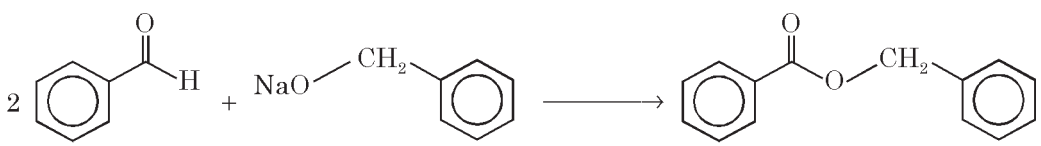
4.2.2.5.1. Chemical Structure



Benzyl benzoate

4.2.2.5.2. Synonyms. Benzoic acid benzyl ester ; Benzoic acid phenyl methyl ester ; Benzylbenzene carboxylate.

4.2.2.5.3. Theory



Benzaldehyde (106)	Sodium benzylate (130)	Benzyl benzoate (212.25)

This is not a direct benzoylation reaction, but benzyl benzoate may be prepared* by the interaction of freshly distilled benzaldehyde with sodium benzylate. It is an exothermic reaction and the temperature of the reaction mixture should be maintained between 50–60°C. The final product is obtained by distillation under reduced pressure and the distillate collected at 184–185°C/15 mm pressure.

4.2.2.5.4 Chemicals Required. Sodium metal = 0.6 g ; Benzyl alcohol = 14 g ; Benzaldehyde = 91 g.

4.2.2.5.5 Procedure. The various steps involved are as stated below :

(1) 0.6 g (0.13 atom) of pure metallic sodium is dissolved by warming slowly and gently for almost 90–100 minutes in 14 g (0.65 mole) of pure benzyl alcohol.

(2) After the mixture has attained the room temperature, the solution is added gradually, in small lots at intervals, with constant stirring, to 91 g (4.3 moles) of pure benzaldehyde (which must contain less than 1% of benzoic acid).

(3) The resulting reaction mixture has a tendency to become warm, but the temperature must be kept slightly below 50–60°C by adequate cooling, if so required. This gives rise to a *pasty gelatinous mass*. After about 90-100 minutes the temperature of the mixture does not rise anymore ; it is subsequently warmed on the water-bath for 1–2 hours, with *occasional* shaking.

(4) The cooled reaction product is treated with 40 ml of water, the layer of oil gets separated, washed carefully once with a second 40 ml portion of water, and finally subjected to distillation under reduced pressure (vacuum).

*Kamm, O., and Kamm W.F., *Org. Syn.* **Coll Vol. I**, 104 (2nd ed.), 1941.

(5) The first and foremost fraction of the distillate essentially comprises of : benzyl alcohol, unchanged benzaldehyde, and a small proportion of water as well.

(6) Consequently, the temperature rises rapidly to the boiling point of *benzyl benzoate*, and at this point in time the new receiver is placed in position. The desired product boils at 184–185°C/mm. (*However, its analysis by saponification has revealed it to contain 99% of benzyl benzoate*).

The yield of benzyl benzoate (bp 184–185°C) is approximately 80 g.

Note : The resulting benzyl benzoate supercools readily, but after solidification does melt within one degree of the highest recorded value (19.4°C) ; and, therefore, does not require any refractionation ordinarily.

4.2.2.5.6 Precautions

(1) Benzyl alcohol must be *free* from impurities, especially aldehyde.

(2) Benzaldehyde should be sufficiently of pure Grade, and must contain less than 1% of benzoic acid as an impurity.

(3) The sequence or order of mixing of reagents and the temperature of ingredients at the time of mixing are the **most** important factors in this synthesis.

(4) The reaction mixture must be maintained below 50-60°C so as to get a better product with a better yield.

4.2.2.5.7 Theoretical Yield/Practical Yield. The theoretical yield may be calculated from the equation under theory (Section 4.2.5.3) as stated below :

212 g of Benzaldehyde on reacting with 130 g of sodium Benzylate

yields Benzyl Benzoate = 212.25 g

$\therefore$ 91 g of Benzaldehyde shall yield Benzyl Benzoate $= \frac{212.25}{212} \times 91 = 91.10$ g

Hence, Theoretical yield of Benzyl Benzoate = **91.10 g**

Reported Practical yield = 80 g

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{80}{91.10} \times 100 =$ **87.81**

4.2.2.5.8 Physical Parameters. Benzyl benzoate is obtained as leaflets or oily liquid, having faint, pleasant aromatic odour with sharp burning taste, mp 21°C ; d_4^{25} 1.118 ; bp_{16} 189–191°C ; sparingly volatile with steam ; n_D^{21} 1.5681. It is found to be insoluble in water or glycerol, but miscible with ethanol, chloroform, ether and oils.

4.2.2.5.9 Uses

(1) It is used as a topical scabicide* and pediculicide.**

(2) It is also employed as an antipedicular agent.

***Scabicide.** An agent that kills mites, especially the causative agent of scabies.

****Pediculicide.** An agent that kills the parasitic insects called '**lice**' which infest humans and other primates.

4.2.2.5.10 Questions for *Viva-Voce*

(1) Why is it required to use pure benzyl alcohol (anhydrous) to prepare sodium benzylate ?

(2) Why is the reaction between benzaldehyde and sodium benzylate has a tendency to become warm ?

(3) What are the chemical constituents present in the first fraction of the distillate ?

(4) What is the temperature at which benzyl benzoate usually distilled in its pure form ?

(5) Why is it not necessary for 'refractionation' of benzyl benzoate obtained in the above experimental procedure ?

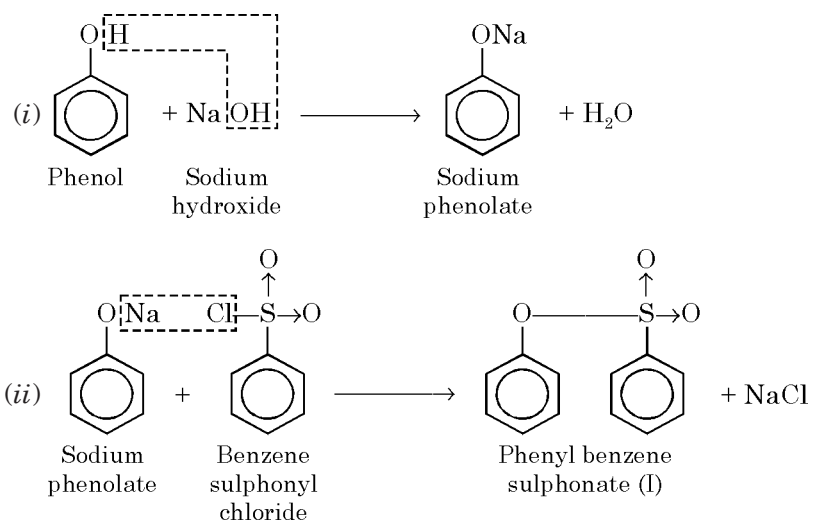
4.3 SULPHONYLATION METHODS

4.3.1 Introduction

Another important aspect of **Schotten-Baumann** reaction is *sulphonylation* whereby benzene sulphonyl chloride, $C_6H_4SO_2Cl$ (*i.e.,* the corresponding '*acid chloride*' of benzene sulphonic acid, $C_6H_4SO_3OH$) is employed instead of benzoyl chloride, and almost similar structural analogues may be obtained.

It has been established experimentally that Schotten-Baumann sulphonylation holds good for *two* different types of organic compounds, namely : (*a*) *Phenols—i.e.,* OH moiety attached directly to an aromatic ring, and (*b*) *Aniline—i.e.,* primary aromatic amine. These reactions are dealt with separately as under :

(*a*) **Sulphonylation with Phenol**

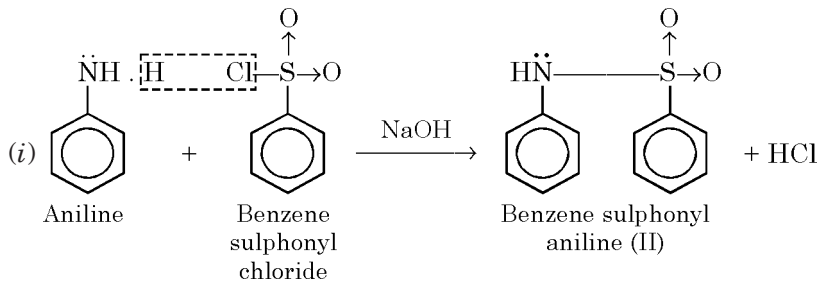


Explanation. The sulphonylation with phenol takes place in *two* steps essentially ; *first*, is the formation of sodium phenolate by the interaction of phenol with an excess of 10% (*w/v*) NaOH solution ; and *secondly*, the reaction between sodium phenolate and a small excess of benzene sulphonyl chloride to give rise to the formation of phenyl benzene sulphonate (I).

Thus, the crystalline ester (I) is separated and the excess of benzene sulphonyl chloride gets hydrolyzed by the alkali producing the **soluble** sodium benzene sulphonate.

(*b*) **Sulphonylation with Aniline or Monomethylaniline**

Explanation. A suspension of freshly redistilled aniline (straw-yellow colour liquid) in sodium hydroxide solution [10% (*w/v*)] when treated in a similar manner with benzene sulphonyl

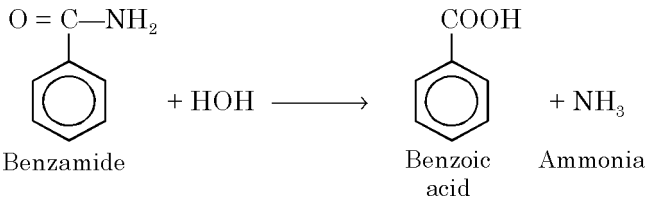


chloride, it yields benzene sulphonyl aniline (II) [Equation (*i*)]. Likewise, when monomethylaniline (*i.e.,* a substituted aniline analogue is treated with benzene sulphonyl chloride, in the presence of NaOH solution, it shall give rise to the formation of benzenesulphonylmethylaniline (III) [Equation (*ii*)]. In other words, these two compounds (II) and (III) may be looked upon as the corresponding *mono*- and *di*-substituted derivatives of benzenesulphonamide, [$C_6H_5SO_2NH_2$] ; and, therefore, known as **benzenesulphonphenylamide** (II) and **benzenesulphonmethylamide** respectively.

4.3.1.1. Similarity with Benzoylation. The most significant point of similarity between benzoylation and sulphonylation is that both of them may be used to accomplish reasonably well defined crystalline derivatives not only of *hydroxyl compounds* but also of *primary* and *secondary amines*. **[Note. It is, however, pertinent to observe here that the tertiary amines cannot be subjected to sulphonylation.]**

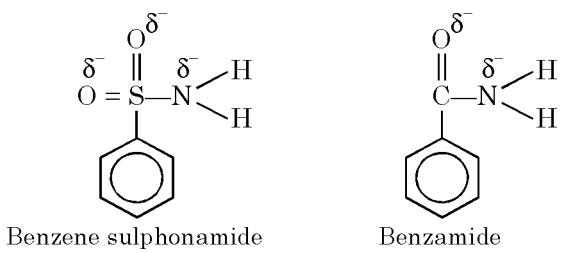
4.3.1.2. Dissimilarity with Benzoylation. It has been observed that there is one vital difference between the '*benzoyl*' and the '*sulphonyl*' derivatives of **amines**. Importantly, when the *primary*- and *secondary*-amines are made to react with **Benzoyl Chloride**, it gives rise to mono-and di-substituted structural analogues of *benzamide* ; and when subjected to treatment with **Benzenesulphonyl Chloride**, yield similar derivatives of *benzene sulphonamide*.

Explanation. Benzamide—a carboxylic acid amide, essentially possesses *very feeble amphoteric properties exclusively*, by virtue of the fact that it undergoes hydrolysis to give the corresponding **acid** and **ammonia** as shown below :



Therefore, **benzamide** is *practically neutral* in character, and its derivatives are virtually *insoluble* in dilute aqueous solutions of acids or alkalis.

Benzenesulphonamide—a sulphonic acid amide, on the contrary is virtually *devoid of basic characteristics*, but **more importantly** has its *acidic characteristics* **enhanced** considerably and significantly as illustrated below :



It is quite evident that the *benzenesulphonamide* is **more acidic** than the amide of an aromatic carboxylic acid *viz., benzamide*, because the **negative charge** is dispersed over two oxygen plus nitrogen instead of over just one oxygen plus nitrogen. Consequently, each of the H-atoms in the $—NH_2$ moiety can in turn display marked and pronounced *acidic properties*. Furthermore, sulphonamides and their corresponding *mono*-substitution derivatives are definitely **acidic** and hence shall undergo dissolution more freely in sodium hydroxide solution, although they are *insoluble in acids* ; however, their *di*-substitution derivatives, having no available acidic H-atoms, are invariably **neutral** in character and, therefore, insoluble in both alkalies and acids.

It is pertinent to mention here that though benzenesulphonyl chloride has for simplicity been used and exemplified in the aforesaid discussion, toluene-*para*-sulphonyl chloride, [$H_3C—C_6H_4—SO_2Cl$], is employed invariably in the laboratory-synthesis, on account of its relatively *much lower cost* as the latter, by virtue of the fact that toluene-*p*-sulphonyl chloride happen to be a by-product in the commercial preparation of saccharin. Toluene *p*-sulphonyl chloride normally reacts promptly with the *amines* in the Schotten-Baumann reaction. However, it does not react to speedily with the *alcohols*, but invariably the reaction may be augmented and promoted significantly by first dissolving the '*acid chloride*' in an **inert-water-soluble solvent** *e.g.*, acetone.

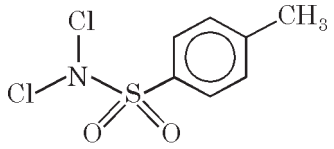
The '**sulphonylation method**' may be used for the syntheses of dichloramine-T and chloramine-T starting from toluene-*p*-sulphonamide and dichloramine-T respectively.

4.3.2 Syntheses of Medicinal Compounds

The following are two patent medicinal compounds, namely : Dichloramine-T and Chloramine-T, which shall be discussed in the sections that follow :

4.3.2.1 Dichloramine-T

4.3.2.2 Chemical Structure



Dichloramine-T

4.3.2.3 Synonyms. N, N-Dichloro-*p*-toluene sulphonamide ; N, N-Dichloro-4-methylbenzene sulphonamide.

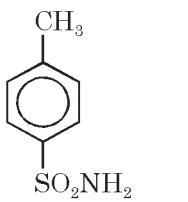
4.3.2.4 Theory. Dichloramine-T may be prepared by the help of a two-step synthesis, namely :

Step I. Preparation of Toluene-*p*-sulphonamide, and

Step II. Preparation of Dichloramine-T from toluene-*p*-sulphonamide.

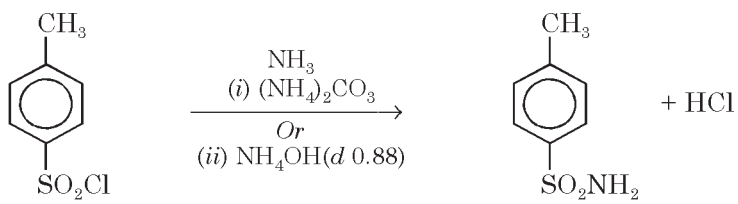
Step I. Toluene-p-Sulphonamide

Chemical Structure



Toluene-*p*-sulphonamide

Theory



Toluene-*p*-sulphonyl chloride (190.65)

Toluene-*p*-sulphonamide (171.15)

Toluene-*p*-sulphonyl chloride either on heating with ammonium carbonate or liquid ammonia replaces the chloro group with an amino moiety to result the formation of toluene-*p*-sulphonamide and a mole of HCl gets eliminated.

Chemicals Required. Toluene-*p*-sulphonyl chloride : 5 g ; Ammonium carbonate : 10 g ; **OR** concentrated Ammonia solution (*d* 0.88) : 15 ml.

Procedure. In actual practice, there are *two* different procedures that are used for the synthesis of toluene-*p*-sulphonamide as given below :

Method–I. The various steps involved are as follows :

(1) Grind together 5 g (0.0525 mol) of toluene-*p*-sulphonyl chloride, and 10 g of ammonium carbonate in a mortar until a fine uniform powder is accomplished.

(2) Transfer the resulting mixture to an evaporating dish and heat the contents over a water-bath for a duration of 1–2 hours, and stir the mixture frequently with a clean stainless-steel spatula.

(3) Allow the resulting mixture to attain room temperature and extract with a little cold water to remove the excess unreacted ammonium salts.

The yield of the crude product (mp 136-137.5°C) is 4.1 g.

Precautions

(1) The two main reactants must be intimately triturated to a fine powder so as to facilitate the conversion to the final desired product.

(2) Constant heating over the water-bath of the mixture is very much important to ascertain completion of reaction.

Recrystallization. The crude product (8.3 g) may be recrystallized from boiling water (100-125 ml), and dry the colourless crystals at 100°C. The yield of pure product (mp 137.5–138°C) is 3.8 g.

Method–II. An alternate equally effective and feasible method for the preparation of toluene-*p*-sulphonamide is as stated below :

(1) Grind 5 g of toluene-*p*-sulphonyl chloride to a fine powder and add to it 15 ml of concentrated ammonia solution (*d* 0.88).

(2) Heat the mixture to boiling in a **Fume Cupboard** and then cool.

(3) Filter the crude product and recrystallize the toluene-*p*-sulphonamide from boiling water (add 0.5 g of decolourizing carbon, if required). The yield of pure product (mp 137.5–138°C) is nearly to that of theoretical yield (4.89 g).

Theoretical Yield/Practical Yield. The theoretical yield is calculated from the equation given under theory as stated below :

190.65 g of Toluene sulphonyl chloride on amination yields

Toluene-*p*-sulphonamide = 171.15 g

∴ 5 g of Toluene-*p*-sulphonyl chloride shall yield

$$\text{Toluene-}p\text{-sulphonamide} = \frac{171.15}{190.65} \times 5 = 4.89 \text{ g}$$

Hence, Theoretical yield of Toluene-*p*-sulphonamide = **4.89 g**

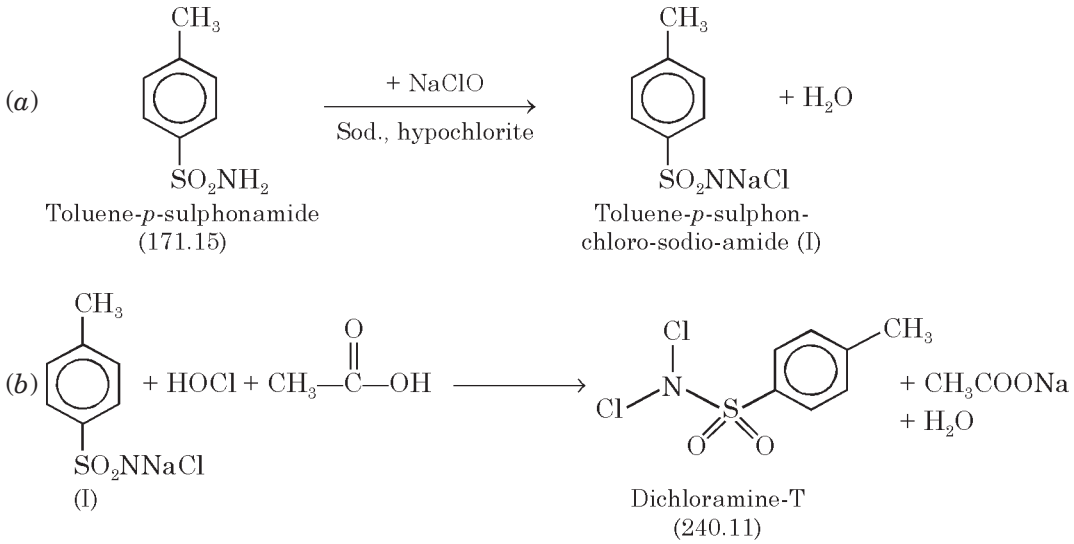
Reported Practical yield = 4.1 g

$$\text{Therefore, Percentage Practical yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

$$= \frac{4.1}{4.89} \times 100 = \mathbf{83.84}$$

Step II. Dichloramine-T

Theory



Toluene-*p*-sulphonamide (171.15)

Toluene-*p*-sulphon-chloro-sodio-amide (I)

(I)

Dichloramine-T (240.11)

Equation (*a*) Toluene-*para*-sulphonamide on dissolution in an excess of sodium hypochlorite solution gives rise to the formation of toluene-*p*-sulphon-chloro-sodio-amide (I)*, which being water-soluble does not ordinarily crystallise out unless and until very concentrated solutions are employed.

Equation (*b*) At this particular stage if a *weak acid, e.g.,* acetic acid is added to the resulting solution of (I) above, the latter compound (*i.e.,* I) readily interacts with the *hypochlorus acid* yielding the **Dichloramine-T** (or Toluene-*p*-sulphon-dichloro amide), which being *water-insoluble* gets separated rapidly.

Chemicals Required. Sodium hypochlorite solution (2 M)** : 80 ml ; Toluene-*p*-sulphonamide : 5 g ; Glacial acetic acid/water (1 : 1) : 50 ml.

Procedure

(1) Dilute 80 ml of **freshly prepared** sodium hypochlorite solution (2 M) with 80 ml of water in a 250 ml beaker.

(2) Add to the above solution 5 g of **finely powdered** toluene-*p*-sulphonamide with constant stirring so as to obtain a rapid clear solution.

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*Compound (I) has a close resemblance to sodium acet-bromoamide, [$CH_3CONNaBr$], which is an **INTERMEDIATE PRODUCT** in Hoffman's primary amine synthesis.

****Sodium Hypochlorite Solution (2 M).** 100 ml : Dissolve 10 g of NaOH in 20 ml water in a 250 ml beaker, cooling the solution, and then adding about 50 g of crushed ice. Now counterpoise the beaker on a rough set of scales, and pass in chlorine from a cylinder until an increase in weight of 72 g is achieved. Make up the volume of the solution to 100 ml and shake thoroughly. The solution should be kept in a cool, dark place, but even then it slowly decomposes.

(3) Cool the resulting solution in ice-water, and initiate addition of 50 ml of a mixture containing equal volumes of glacial acetic acid and water, in small lots at intervals, with constant stirring until complete precipitation takes place.

(4) Dichloramine-T separates at first as a **fine emulsion**, that readily forms brittle colourless crystals.

(5) Crystals are filtered on the Büchner funnel with a suction, washed well with water, drained thoroughly, and dried without any lapse of time preferably in a desiccator or between the folds of filter paper.

The yeild of crude product (mp 82–82.5°C) is approximately 6.5 g.

Precautions

(1) Always make use of (2 M) sodium hypochlorite solution for the synthesis that has been prepared afresh.

(2) Toluene-*p*-sulphonamide must be pulverised to fine powder before it is used in the reaction to get better yield.

(3) The crude product must be dried either in a desiccator or between the folds of filter paper as quickly as possible to avoid possible decomposition. (**Sensitive Product**)

Recrystallization. The crude product may be recrystallized from minimum quantity of petroleum ether (60–80°C). It is obtained as needles (mp 82.5–83°C) upto 6.3 g.

Theoretical Yield/Practical Yield. The theoretical yield may be calculated from the equations (*a*) and (*b*) under theory as given below :

171.15 g of Toluene-*p*-sulphonamide on reaction with sodium hypochlorite and acetic acid yields Dichloramine-T = 240.11 g

$\therefore$ 5 g of Toluene-*p*-sulphonamide shall yield

$$\text{Dichloramine-T} = \frac{240.11}{171.15} \times 5 = 7.01 \text{ g}$$

Hence, Theoretical yield of Dichloramine-T = **7.01 g**

Reported Practical yield = 6.5 g

Therefore, Percentage Practical yield

$$= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

$$= \frac{6.5}{7.01} \times 100 = \mathbf{92.72}$$

Physical Parameters. It is obtained as prisms from a mixture of chloroform and petroleum ether (60–80°C) having mp 83°C. It has a strong odour of chlorine, and gets decomposed on exposure to air with loss of Cl_2 (mp 80°C). It is almost insoluble in water and decomposed by alcohol when warmed. 1 g Dissolves in about 1 ml benzene, 1 ml chloroform, 2.5 ml CCl_4 ; soluble in eucalyptol, chlorinated paraffin hydrocarbons, glacial acetic acid ; and slightly soluble in petroleum ether. It contains 28–30% of active available chlorine.

Uses

(1) A 1% (*w/v*) solution in chlorinated paraffin is employed for application of mucous membranes as a *germicide* ; and a 5% (*w/v*) solution in the same solvent is invariably used in dressing wounds as an *antibacterial agent*.

(2) As it is far less alkaline than Sodium Hypochlorite Solution NF, it finds its application as an antiseptic and disinfectant.

Questions for *Viva-Voce*

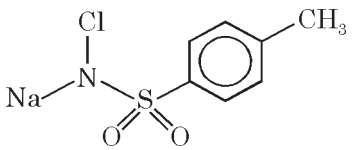
(1) What is the name of the intermediate product obtained by the interaction of Toluene-*p*-sulphonamide and sodium hypochlorite ?

(2) Why is it necessary to carry out the acidification of the resulting '*intermediate product*' to obtain Dichloramine-T ?

(3) Why is it required to dry the crude product either in a desiccator or between the folds of filter paper quickly ?

4.3.2.2 Chloramine-T

4.3.2.2.1 Chemical Structure



Chloramine-T

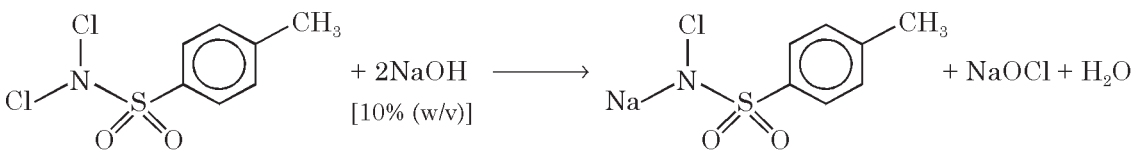
4.3.2.2.2 Synonyms. Chloramine ; Chloraseptine ; Chlorazene ; Gansil ; Mianine ; Tochlorine ; Tolamine.

Chloramine-T may be prepared by *two* methods, namely :

Method–I. From Dichloramine-T, and

Method–II. Direct from Toluene-*p*-Sulphonamide.

4.3.2.2.3 Theory (Method–I). From Dichloramine-T



Dichloramine-T (240.11) Chloramine-T (227.65)

Dichloramine-T when heated with sufficient amount of 10% (*w/v*) sodium hydroxide solution it gives rise to the formation chloramine-T and a mole each of sodium hypochlorite and water.

Chemicals Required. Dichloramine-T : 6 g ; Sodium Hydroxide Solution [10% (*w/v*)] : 40 ml.

Procedure

(1) Heat 40 ml of sodium hydroxide solution in a 250 ml beaker over an asbestos-wire gauze gently until the solution is almost boiling.

(2) To the above solution add 7 g of the crude product *i.e.,* Dichloramine-T, in small lots at intervals with constant stirring.

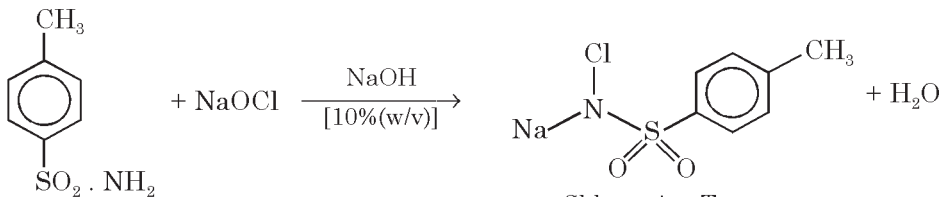
(3) When the addition is complete, cool the reaction mixture in ice-cold water, whereupon the desired product chloramine-T shall separate out as crystals readily.

(4) Filter the crystalline product on the Büchner funnel with the suction and drain thoroughly. The yield of the sufficiently pure product is almost near to the *theoretical yield*. It may be dried with drying-paper or in a $CaCl_2$—desiccator or in a vacuum (*i.e.,* reduced pressure). The yield of the product is approximately 5.5 g which does not exhibit any definite mp.

Note : (1) The product may be recrystallized, if desired, from a small quantity of hot water, and

(2) The product is **NOT** dried over **sulphuric acid** in a desiccator as it loses water of crystallization rapidly.

Theory (Method–II). From Toluene-*p*-sulphonamide



Toluene-*p*-sulphonamide (171.15)

Chloramine-T (227.65)

The interaction between toluene-*p*-sulphonamide with freshly prepared sodium hypochlorite solution (2 M) in the presence of 10% NaOH solution results into the formation of chloramine-T, and a mole of H_2O gets eliminated.

Chemicals Required. Toluene-*p*-sulphonamide : 5 g ; Freshly prepared 2 M Sodium Hypochlorite solution : 45 ml ; Sodium Hydroxide solution [10% (*w/v*)] : 40 ml.

Procedure

(1) First of all mix together 45 ml of 2 M sodium hypochlorite solution and 40 ml of 10% NaOH solution in a 250 ml conical flask.

(2) Add to the above solution quickly 5 g of finely powdered toluene-*p*-sulphonamide and cork the flask securedly.

(3) Shake the contents of the flask vigorously by holding the cork-in-position for 5–8 minutes, whereupon the toluene-*p*-sulphonamide shall undergo complete dissolution ; and at the same time a white crystalline chloramine-T would appear almost distinctly.

(4) Warm the contents of the flask until a clear solution is obtained ; so as to ensure removal of any unreacted dichloramine-T, and then cool.

(5) Chloramine-T will start separating out on gradual cooling in the form of needles ; while on '**sudden-chilling**' in the form of distinct characteristic leaflets.

(6) Filter, drain and dry over $CaCl_2$ in a desiccator. The yield of the product is 6.3 g having no definite mp.

Method–I. Theoretical Yield/Practical Yield. The theoretical yield is calculated from the equation given under theory (Method–I) as stated below :

240.11 g of Dichloramine-T on treatment with NaOH solution yields

Chloramine-T = 227.65 g

$\therefore$ 6 g of Dichloramine-T shall yield Chloramine-T $= \frac{227.65}{240.11} \times 6 = 5.69$ g

Hence, Theoretical yield of Chloramine-T = **5.69 g**

Reported Practical yield = 5.5 g

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{5.5}{5.69} \times 100 =$ **96.66**

Method–II. Theretical Yield/Practical Yield. The theoretical yield is calculated from the equation given under theory (Method–II) as mentioned below :

171.15 g of Toluene-*p*-sulphonamide on treatment with sodium

Hypochlorite gives Chloramine-T = 227.65 g

$\therefore$ 5 g of Toluene-*p*-sulphonamide yields Chloramine-T $= \frac{227.65}{171.15} \times 5 = 6.65$ g

Hence, Theoratical yield of Chloramine-T = **6.65 g**

Reported Practical yield = 6.3 g

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{6.3}{6.65} \times 100 =$ **94.73**

4.3.2.2.4 Physical Parameters. It is obtained as trihydrate prisms that lose water on drying. It gets decomposed gradually on being exposed to air. It is fairly soluble in water ; practically insoluble in benzene, chloroform, ether ; and gets decomposed by alcohol. It contains 11.5–13 per cent of active available chlorine.

4.3.2.2.5 Uses

(1) It is mostly employed as an antiseptic and disinfectant but is less irritant in nature.

(2) It is invariably applied to mucous membranes as a 0.1% aqueous solution.

(3) It is also used to irrigate or dress wounds as a 1% (*w/v*) solution.

4.3.2.8 Questions for *Viva-Voce*

(1) What are the two different methods for the synthesis of the antibacterial agent chloramine-T ?

(2) What is the advantage of one method over the other ?

(3) Does the second method comply to the Schotten-Baumann reaction ?

4.4 BROMINATION METHODS

4.4.1 Introduction

Generally, aromatic hydrocarbons or their corresponding substituted derivatives upon interaction with bromine in the absence of light (dark) but in the presence of specific *halogen carriers*, namely : iron, iodine, pyridine or aluminium amalgam invariably result into the formation of appropriate bromo-substituted derivatives. At an initial stage a *mono-bromo derivative* is formed which on subsequent treatment with bromine ultimately give rise to the formation of the respective *polybromo derivative.*

4.4.1.1 Mechanism of Bromination

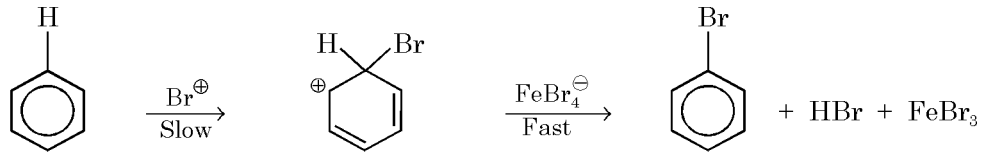
Broadly speaking *'bromination'* is an electrophilic substitution reaction. The major role of the *halogen carriers* is to generate strategically a **bromonium ion electrophile** that eventually attacks the nucleus at the particular site of *maximum-electron-density.*

Examples

(*i*) Bromination of *benzene* yields *bromobenzene* as given below :

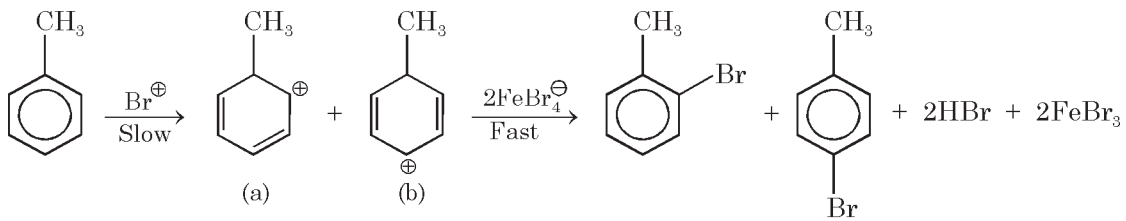
$$Br_2 + FeBr_3 \longrightarrow Br^{\oplus} + FeBr_4^{\ominus}$$

Bromine — Ferric bromide — Bromonium ion — Ferricbromobromide ion



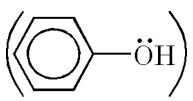
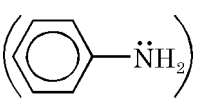
Benzene — A Resonance stabilized intermediate — Bromobenzene

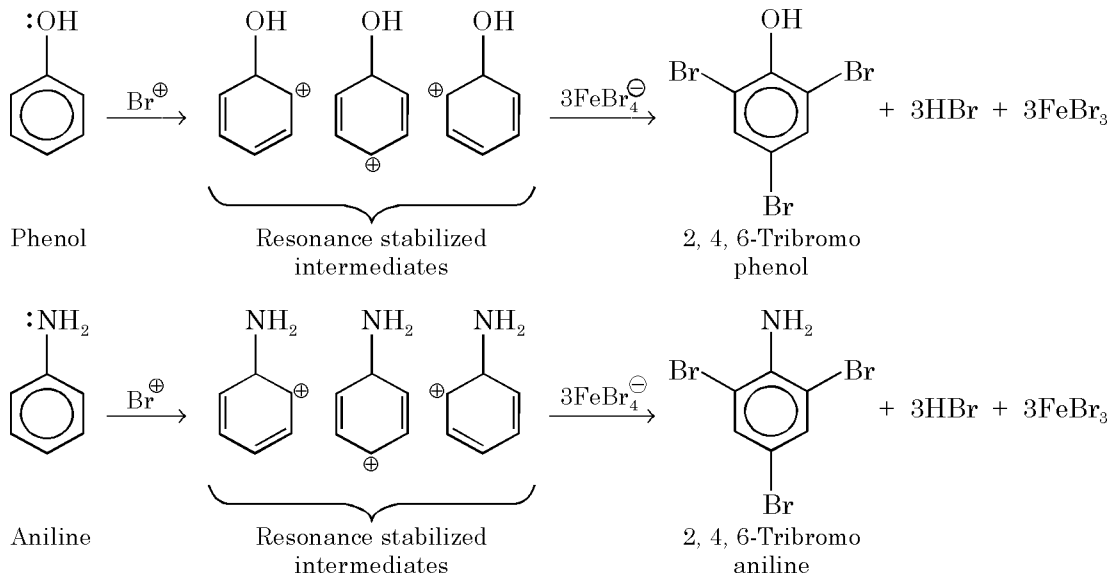
(*ii*) Bromination of *toluene* (next higher homologue) yields a mixture of *ortho-* and *para-bromotoluenes* as shown below :



(a) (b)

Toluene — *o*-and *p*- Resonance stabilized intermediates of toluene — *o*-Bromo toluene — *p*-Bromo toluene

However, the highly activated compounds like phenol  or aniline  react readily and completely with bromine in a medium of acetic acid to result the corresponding 2, 4, 6-tribromo derivatives as stated under :

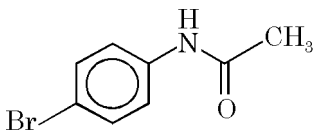


4.4.2 Synthesis of Medicinal Compounds

Following are a few typical examples of medicinal compounds that are prepared by the help of bromination method, namely : *para*-Bromoacetanilide ; *para*-Bromophenol ; Tetrabromofluorescein (or Eosin).

4.4.2.1 *para*-Bromoacetanilide

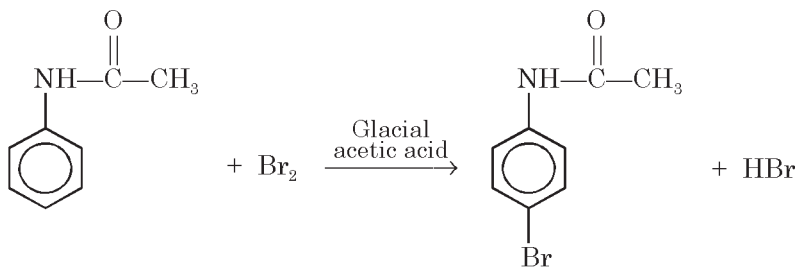
4.4.2.1.1 Chemical Structure



para-Bromoacetanilide

4.4.2.1.2 Synonyms. N-(4-Bromophenyl) acetamide ; 4′-Bromoacetanilide ; Bromoanilide ; Antisepsin ; Bromoantifebrin.

4.4.2.1.3 Theory



Acetanilide (*i.e.,* the acetyl derivative of aniline) on being subjected to bromination (with Br_2) in a medium of glacial acetic acid gives rise to the *para*-bromoacetanilide with the liberation of a mole of HBr. The acetamido (—$NHCOCH_3$) is an **ortho, para director** function ; hence, the incoming bromo moiety shall yield both *ortho*- and *para*-isomers. The latter is produced predominantly (upto 90%) as a white solid.

4.4.2.1.4 Chemicals Required. Acetanilide : 4.5 g ; Bromine : 1.8 ml ; Glacial Acetic Acid : 25 ml ; Sodium bisulphite : 5 g ; Rectified spirit : 30 ml.

4.4.2.1.5 Procedure. The various steps followed are as a stated below :

(1) Dissolve 4.5 g of finely powdered acetanilide in 15 ml of glacial acetic acid in a 250 ml conical flask.

(2) Transfer 1.8 ml of bromine into a 100 ml conical flask containing 10 ml of glacial acetic acid. Swirl the contents of the flask and take it in a 25 ml burette.

(3) Chill the contents of the flask containing acetanilide (1) in an ice-bath and add to it the bromine solution from the burette (2) drop-wise with constant stirring very gradually.

(4) The resulting solution should distinctly appear as an *orange colour* due to the presence of a slight excess of bromine. It is now allowed to stay at room temperature for a duration of 30–40 minutes.

(5) The contents of the flask are poured directly into a 500 ml beaker having 200 ml of ice-cold water in one-go. The conical flask is further rinsed with 50 ml of cold water and then transferred into the beaker.

(6) At this stage the crude *p*-bromoacetanilide gets separated as a white solid, stir it well. In case, the colour of the solution is peristently yellow in appearance, add 4–5 g of sodium bisulphate with constant stirring so as to bleach the undesired colouration.

(7) Filter the crude product in a Büchner funnel with appropriate suction, wash the residue with a spray of cold water from a wash-bottle, drain well and dry in an oven previously maintained at 100°C.

The yield of crude product is 6.2 g having mp 165–166°C.

4.4.2.1.6 Precautions

(1) The acetanilide solution in glacial acetic acid must be cooled to about 0–5°C before the addition of bromine/acetic acid solution to it as the reaction is exothermic in nature. The bromination must be allowed to complete by maintaining the reaction mixture *in situ* at ambient temperature for 30–40 minutes.

(2) Addition of 4–5 g of sodium bisulphite acts as a bleaching agent to remove the persistent yellow colouration of the crude *p*-bromoacetanilide reaction mixture.

4.4.2.1.7 Recrystallization. The crude product (3.0 g) may be recrystallized from rectified spirit (25 ml) either at room temperature or slightly warming it in an electric-water bath. The yield of pure colourless *para*-bromoacetanilide is 2.8 g (mp 166.5–167°C).

4.4.2.1.8 Theoretical Yield/Practical Yield. The theoretical yield is calculated from the equation under theory (section 4.4.2.4) as given below :

135.17 g of Acetanilide on being reacted with 1.8 ml of Br_2

yields *p*-Bromoacetanilide = 214.06 g

$\therefore$ 6 g of Acetanilide shall yield *p*-Bromoacetanilide $= \frac{214.06}{135.17} \times 6 = 9.50$ g

Hence, Theoretical yield of *p*-Bromoacetanilide = **9.50 g**

Reported Practical Yield = 6.2 g

Therefore, Percentage Practical Yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{6.2}{9.5} \times 100 =$ **65.26.**

4.4.2.1.9 Physical Parameters

It is obtained as crystals from 95% alcohol (mp 168°C) with previous softening of the solid mass. It is found to be practically insoluble in cold water ; sparingly soluble in hot water ; soluble in benzene, chloroform, ethylacetate ; and moderately soluble in ethanol.

4.4.2.1.10 Uses

(1) It is used as an analgesic.

(2) It is also employed as an antipyretic.

4.4.2.1.11 Questions for *Viva-Voce*

(1) Why is it necessary to add the Br_2 solution in acetic acid to the acetanilid solution at 0–5°C ?

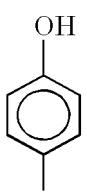
(2) Why does the bromination take place in an acidic medium ?

(3) What is the specific role of sodium bisulphite ?

(4) Why should Br_2 be present always in slight excess in the reaction mixture ?

4.4.2.2 *para*-Bromophenol

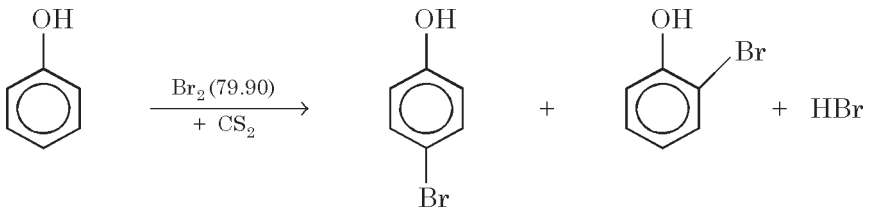
4.4.2.2.1 Chemical Structure



para-Bromophenol

4.4.2.2.2 Synonym. 4-Bromophenol ;

4.4.2.2.3 Theory



Phenol (94.11) — *para*-Bromophenol [~ 90%] (173.01) — *ortho*-Bromophenol [~ 10%]

Phenol is taken up in dry carbon disulphide (CS_2) which is subsequently reacted with a solution of Br_2 in CS_2 at a controlled temperature ranging between 0–5°C with vigorous constant stirring in an **efficient fume cupboard.** *para*-Bromophenol is obtained as the major product, whereas *ortho*-bromophenol is also produced inevitably to a much lesser extent.

4.4.2.2.4 Chemicals Required. Phenol : 9.4 g ; Carbon disulphide : 1.5 ml ; Bromine : 16 g (5.1 ml) ; Chloroform : 30 ml.

4.4.2.2.5 Procedure

(1) Equip in a fume cupboard a 250-ml three-necked flask duly fitted with a reflux condenser, a mechanical stirrer and a separatory funnel.

(2) The top-end of the reflux condenser must be adequately attached by a *calcium chloride guard-tube* which is duly connected by means of a glass tube to a funnel just immersed in a beaker filled with about 150 ml water for absorption of hydrogen bromide gas (HBr).

(3) Transfer 9.4 g (1 mole) of phenol dissolved in 10 ml of dry carbon disulphide in the flask. Switch on the mechanical stirrer and cool the contents of the flask below 5°C by placing it in a freezing mixture of ice and salt.

(4) Add with a gradual pace from the separatory funnel a solution of 5.1 ml (16 g ; 1 mole) of bromine in 5 ml of CS_2, within a span of 120 minutes.

(5) Arrange the 3-necked flask for distillation under vacuo, and stopper the remaining two sockets securedly.

(6) Connect a condenser set for downward distillation to the *Claisen still-head* and subsequently attach the improvised device for the absorption of HBr vapours evolved duly to the side-arm of the receiver adapter.

(7) First of all distill off the CS_2 at atmospheric pressure on a water bath maintained at 60°C.

(8) Remove the HBr-absorption device, and insert a capillary leak and a thermometer (0–360°C) in position duly into the Claisen still-head sockets. Now, proceed with the distillation *under vacuo* over an oil-bath.

(9) Precisely collect *two* fractions as stated under :

(*a*) *At bp below 145°C / 25–30 mm Hg.* Which being an inseparable mixture of *ortho*- and *para*- bromophenols *i.e.,* the two isomers (2.3–3.2 g), and

(*b*) *At bp 145–150°C / 25–30 mm Hg.* Which being a reasonably pure *para*-bromophenol.

However, the residue left in the flask essentially consists of certain *higher boiling range 2, 4-dibromophenol.*

(10) The *p*-bromophenol obtained in [9(*b*)] above usually gets solidified on cooling to a solid white mass that invariably contains traces of an oily substance ; which may be removed either by centrifugation or by spreading on a *porous tile.*

The yield of the crude product (mp 62–62.5°C) is 14.2 g.

4.4.2.2.6 Precautions

(1) The preparation must be performed in a fairly efficient fume cupboard.

(2) The hydrogen bromide (HBr) gas must be absorbed by the prescribed device adequately.

(3) The distillation of the final product is always carried out by an equally efficient assembly under perfect reduced pressure as stated above.

(4) The addition of bromine solution to the phenol solution should be done *cautiously, slowly* and *carefully* over 2 hours in small lots at intervals at 0—5°C.

4.4.2.2.7 Recrystallization. A portion of the crude product is dissolved in a minimum quantity of chloroform and the pure product gets crystallized having mp 63–64°C.

4.4.2.2.8 Theoretical Yield/Practical Yield. The theoretical yield is calculated from the equation given under theory (section 4.4.2.2.3 as stated below :

94.11 g of Phenol upon bromination with 79.90 g of Br_2 yields

p-Bromophenol = 173.01 g

$\therefore$ 9.4 g of Phenol shall produce *p*-Bromophenol $= \frac{173.01}{94.11} \times 9.4 =$ **17.28 g**

Reported Practical yield = 14.2 g

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{14.2}{17.28} \times 100 =$ **82.17**

4.4.2.2.9 Physical Parameters. It is obtained as tetragonal bipyramidal crystals from chloroform of ether. Its physical constants are : mp 64°C ; bp 238°C ; d^{15} 1.840 ; and d^{80} 1.5875. It has been observed that even the presence of small amounts of water depress the *mp* considerably ; and may prevent crystallization. It is soluble in 7 parts of water, freely soluble in ethanol, chloroform, ether and glacial acetic acid.

4.4.2.2.10 Uses

(1) *para-Bromophenol* is mostly used as a disinfectant.

(2) It is invariably employed as a disinfectant especially for equipments or surfaces rather than in or on the body.

4.4.2.2.11 Questions for *Viva-Voce*

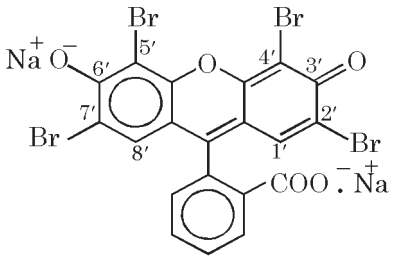
(1) Why is it absolutely necessary to add bromine solution in CS_2 to a chilled solution of phenol in CS_2 very slowly with vigorous stirring over a period of 2 hours ?

(2) How best can one trap the generated HBr gas in a laboratory experimental set-up ? Explain.

(3) What are the *three* distinct fractions collected by distillation of the completed reaction mixture ? Explain.

4.4.2.3 2′, 4′, 5′, 7′-Tetrabromofluorescein

4.4.2.3.1 Chemical Structure



2′, 4′, 5′, 7′-Tetrabromofluorescein

4.4.2.3.2 Synonyms. Eosine Yellowish-(YS) ; 2′, 4′, 5′, 7′-Tetrabromo-3′, 6′-dihydroxyspiro [isobenzofuran]- 1 (3H), 9′-[9H] xanthen]-3-one disodium salt ;

4.4.2.3.3 Theory

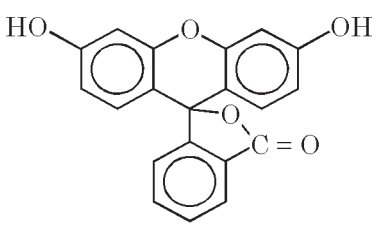
It is a two-step preparation, namely :

(*i*) Preparation of Fluorescein, and

(*ii*) Bromination of Fluorescein to Eosin.

Step-I. Preparation of Fluorescein.

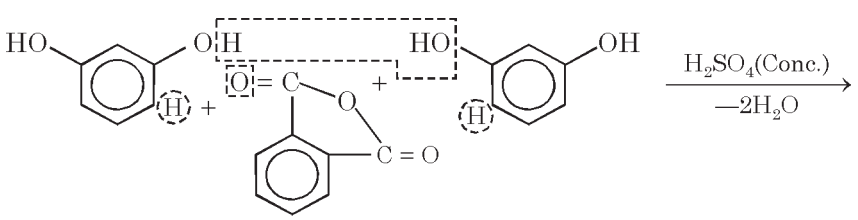
1. Chemical Structure



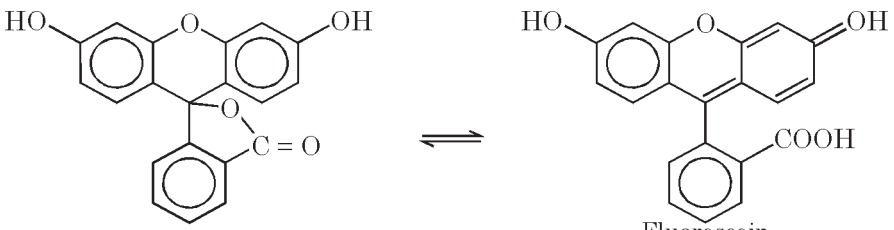
Fluorescein

2. Synonyms. Resorcinolphthalein ; 2-(3, 6-Dihydroxy-9H-xanthen-9-yl) benzoic acid ;

3. Theory



Resorcinol (110.11) | Phthalic anhydride (148.12) | Resorcinol (110.11)



Fluorescein (*enol*-Form) (334.33)

Fluorescein (*keto*-Form)

Resorcinol and phthalic anhydride interact in the presence of a strong dehydrating agent, such as : concentrated sulphuric acid to give a condensed product fluorescein with the elimination of two moles of water. Fluorescein exhibits *keto-enol* tautomerism and the *two* forms do exist as given above.

4. Chemicals Required. Phthalic anhydride (powder) : 5 g ; Resorcinol : 7.5 g ; Sulphuric Acid (Conc.) = 2 – 3 ml ; Dilute NaOH solution = q.s. ; Dilute HCl : q.s. ;

5. Procedure. The various steps involved are as given below :

(1) Mix thoroughly 5 g of phthalic anhydride powder and 7.5 g of resorcinol in a dry 100-ml round bottom flask fitted with an air condenser.

(2) Hold the flask in position in an oil-bath and commence heating slowly till the mixture starts melting.

(3) Add 2-3 ml of concentrated sulphuric acid to the reaction mixture and continue heating it for 3-4 hours by maintaining the temperature of the oil-bath at 180 ± 3°C. During the course of heating the resulting mixture turns viscous and practically a semi-solid mass.

(4) Discontinue the heating-process, allow the mass to attain ambient temperature ; and dissolve the solidified product in dilute sodium hydroxide solution in 4 – 5 successive instalments of dilute NaOH solution (30–40 ml each).

(5) After complete extraction of the solid mass from the flask, the resulting solution is neutralized carefully with dilute HCl with constant stirring when fluorescein gets precipitated apparently.

(6) Cool the contents of the flask in an ice-bath and filter the crude fluorescein in a Büchner funnel with suction, wash with a little cold water, drain well and finally dry in an electric oven maintained at 100°C.

The yield of crude product (mp 124–125°C) is 8.8 g.

6. Precautions

(1) Both phthalic anhydride and resorcinol should be powdered individually before mixing and starting the reaction.

(2) All glass apparatus must be perfectly dry so that concentrated sulphuric acid used in the reaction is fully utilized in the removal of two moles of water.

(3) Extraction of the semi-solid mass with dilute NaOH solution is to be repeated till such time when almost every small bit of it undergoes dissolution.

(4) Subsequent acidification with dilute HCl is to be carried out carefully to regenerate the fluorescein as a precipitate.

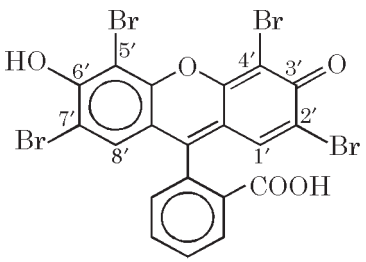
7. Recrystallization. Crude fluorescein may be recrystallized by dissolving a small portion of it again in dilute NaOH solution and reprecipitating it with dilute HCl solution.

The pure fluorescein has mp 125—127°C.

8. Physical Parameters. It is obtained as a bright yellow powder, mp 125–127°C. It is found to be practically insoluble in water, but soluble in alkali carbonates, or hydroxides, alcohol and ether.

Step II. Preparation of Tetrabromofluorescein

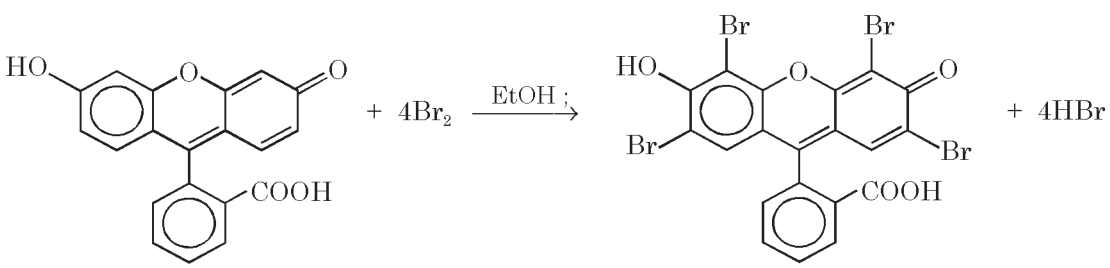
1. Chemical Structure



2′, 4′, 5′, 7′-Tetrabromofluorecein

2. Synonyms. Eosine ; Eosin ; Bromoeosine ;

3. Theory



Fluorecein (334.33) Bromine Eosin (647.86)

Fluorescein is dissolved in ethanol and the solution is chilled between 0–5°C in an ice-bath. Bromination of fluorescein is an exothermic reaction ; and when half of the requisite quantum of bromine is added the solution becomes clear in appearance due to the formation of dibromofluorescein which being soluble in ethanol. Further addition of bromine gives rise to the corresponding tetrabromoderivative (eosin)), which being insoluble in ethanol separates out.

4. Chemicals Required. Fluorescein : 5 g ; Bromine : 3.7 ml (11.6g) ; Rectified alcohol (95% v/v) : 25 ml ;

5. Procedure

(1) Suspend 5 g fluorescein in 25 ml rectified spirit (alcohol) in a 100-ml round bottom flask ; and chill the contents of the flask in an ice-bath.

(2) Add to the fluorescein solution 3.7 ml of bromine from a burette in small lots at intervals with constant vigorous shaking. It is an exothermic reaction and, therefore, the addition of Br_2 must be very slow and gradual.

(3) When one-half of Br_2 has been added a clear solution is obtained.

(4) Continue adding the remaining portion of Br_2 gradually with stirring, the appearance of the tetrabromo derivative (eosin) which being insoluble in rectified alcohol shall separate out instantly. Allow it to stand for 2 hours with occasional shaking.

(5) Filter the product in a Büchner funnel, wash with a little alcohol and dry in an oven maintained at 100°C.

The yield of eosin is 9.3 g.

6. Precautions

(*i*) The addition of bromine solution to fluorescein solution should be done very slowly with constant stirring, because the reaction is exothermic in nature.

(*ii*) After the complete addition of bromine the resulting mixture should be allowed to stand for 2 hours with occasional shaking so as to complete the bromination.

7. Theoretical Yield/Practical Yield. The theoretical yield is calculated from the equation under theory [Step-II (3)] :

334.33 g of Fluorescein on bromination yields Eosin = 647.86 g

$\therefore$ 5 g of Fluorescein shall yield Eosin $= \dfrac{647.86}{334.33} \times 5 = 9.69$ g

Hence, theoretical yield of Eosin = **9.69 g**

Therefore, Percentage Practical yield $= \dfrac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \dfrac{9.3}{9.69} \times 100 =$ **95.97**

8. Physical Parameters. It is obtained as brownish-red powder, freely soluble in water and less in ethanol ; and is insoluble in ether. The concentrated aqueous solution is deep brownish-red, the dilute (1 : 500) solution is yellowish-red with greenish fluorescence ; and the alcoholic solution exhibits a strong green fluorescence.

9. Uses

(*i*) It is frequently employed in microbiological differential media.

(*ii*) It is also used as biological stain.

(*iii*) It has been duly approved by FDA* for use in drugs and cosmetics except for use in eye area.

10. Questions for *Viva-Voce*

(*i*) Why does addition of half the required quantity of Br_2 give a completely soluble product ?

(*ii*) Explain why bromination of fluorescein is an exothermic reaction.

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*__FDA.__ Federal Drug Authority (USA).

4.5 CONDENSATION REACTIONS

Condensation, is a type of reaction in which two or more molecules of the same substance react with each other and form a new and heavier substance with distinct and different chemical properties.

There are several types of condensation reactions that occur in organic chemistry ; however, the following *three* specific condensation reactions shall be dealt with in sufficient details along with a typical example, namely :

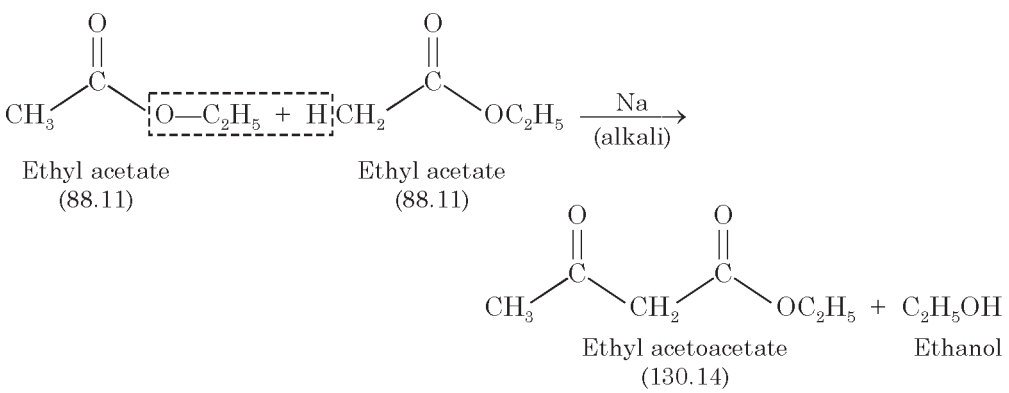
(*i*) Claisen condensation,

(*ii*) Knoevenagel condensation, and

(*iii*) Pechmann condensation.

4.5.1 Claisen Condensation*

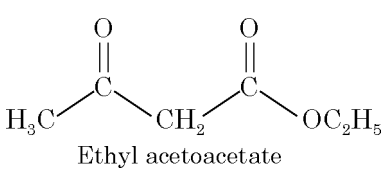
Claisen condensation is also termed as *'acetoacetic ester condensation'.* It is essentially a base-catalyzed condensation of an ester containing an α–hydrogen atom with a molecule of the same ester or a different one to give β-keto esters :



Thus, ethylacetoacetate is an outcome of Claisen condensation of two molecules of ethyl acetate in the presence of alkali to form a β-keto compound.

4.5.1.1 Ethyl Acetoacetate

4.5.1.2 Chemical Structure



*Claisen, L., O. Lowman, *Ber.* **20**, 651 (1887).

Hauser, C.R., B.E. Hudson, *Org. React.* **1.** 266-322 (1942).

Garst, J.F., *J. Chem. Ed.,* **56.** 721 (1979).

Davis, B.R., Garatt, P.J., *Comp. Org. Syn.* **2.** 795–805 (1991).

4.5.1.3 Synonyms

Acetoacetic ester ; Ethyl-3-oxobutanoate ; 3-Oxobutanoic acid ethyl ester ; Acetoacetic acid ethyl ester ;

4.5.1.4 Theory

Please refer to the reaction as given under section 4.5.1.

In this instance, two moles of ethyl acetate get condensed in the presence of alkali to give rise to the formation of ethyl acetoacetate plus one mole of ethanol gets eliminated.

4.5.1.5 Chemicals Required

Ethyl acetate : 73.6 ml ; Sodium wire : 6.4 g ; Acetic acid (5%) : 36 ml ; Sodium chloride : q.s. ;

4.5.1.6 Procedure. The various steps are as follows :

(1) Transfer 73.6 ml of dry and pure ethyl acetate in a 500 ml round bottom flask and add to it 6.4 g of freshly drawn clean sodium wire.

(2) Fit a reflux condenser to the flask and warm the contents of the flask gently on an electric water bath (bp; ethyl acetate 77°C) *for a few minutes only.*

(3) Once the reaction commences, stop-warming and maintain the flask in a cold-water bath, as the reaction is exothermic in nature. Meanwhile, swirl the contents of the flask frequently ; and when the vigorous reaction comes to an end reflux the resulting reaction mixture gently over a water bath for 2 hours so as to complete the reaction (or until all the sodium metal has dissolved).

(4) The resulting solution attains a red colouration, acidify it carefully by adding acetic acid (50%), about 36 ml is required.

(5) Add sufficient solid sodium chloride to saturate the resulting solution when the desired ethyl acetoacetate separates out as the upper layer.

(6) Separate the upper layer using a separating funnel, transfer to a clean beaker, keep it in a desiccator charged with dry $CaCl_2$ overnight to dry up the ester.

(7) Distill the dried ester under vacuo when the unreacted ethyl acetate distills over as the first fraction (ethyl acetate : bp 77°C ; and ethyl acetoacetate bp 180.8°C). The subsequent fraction is of pure ethyl acetoacetate which may be collected at 76-80°C/ 18 mm Hg ; or 80-84°C/20 mm Hg ; or 86-90°/30 mm Hg ; or 90-94°C/40 mm Hg.

The yield of pure ethyl acetoacetate is 14.4 g.

4.5.1.7 Precautions

(1) The reaction is to be carried out in absolute dry conditions only so as order to avoid explosion, because sodium metal wire is used to afford an alkaline medium.

(2) Acidification of the final reaction mixture is to be done very carefully with acetic acid (50%).

(3) Addition of solid NaCl is added to absorb the water content and liberate the desired product exclusively as the upper layer.

(4) The two esters *i.e.,* ethyl acetate (unreacted) and ethyl acetoacetate (desired product) has a large difference in their bp ; and hence could be distilled off quite easily and conveniently.

4.5.1.8 Theoretical Yield/Practical Yield

The theoretical yield is calculated from the equation under section 4.5.1 as given below :

176.22 g of Ethyl acetate by Claisen Condensation yields

Ethyl acetoacetate = 130.14 g

66.09 g (73.6 ml) of Ethylacetate shall yield Ethyl acetoacetate

$$= \frac{130.14}{176.22} \times 66.09 = 48.80 \text{ g}$$

Hence, theoretical yield of Ethyl Acetoacetate = **48.80 g**

Reported Practical yield = 14.4 g

The before, Percentage Practical yield

$$= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

$$= \frac{14.4}{48.8} \times 100 = \mathbf{29.51}$$

4.5.1.9 Physical Parameters

It has an agreeable odour having mp –45°C. It has d_4^{25} 1.0213 ; bp_{760} 180.8° ; n_D^{20} 1.41937. It is found to be soluble in about 35 parts of water ; and miscible with the usual organic solvents.

4.5.1.10 Uses

(1) It is used as a pharmaceutical aid (flavour).

(2) It is also employed as an ingredient in perfumes.

4.5.1.11 Questions for *Viva-Voce*

(1) How does Na metal act as an alkaline medium ?

(2) How does Na metal undergoes dissolution in the reaction mixture ?

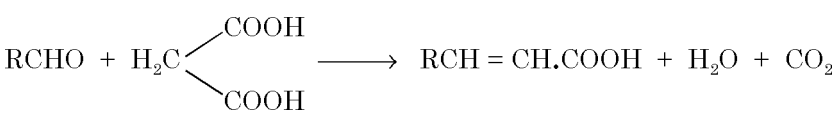
(3) Why is it necessary to carry out of the acidification with acetic acid (50%).

(4) How would you separate the unreacted ethyl acetate from the desired product ethyl acetoacetate ?

4.5.2 Knoevenagel Condensation*

Knoevenagel condensation is also known as **'Doebner Condensation'.**

In this particular instance, the condensation of aldehydes or ketones normally take place with active methylene compounds in the presence of either amines or ammonia ; however, the usage of malonic acid and pyridine is commonly known as the **Doebner** modification. Thus, we have :



*Knoevenagel, E., *Ber.* **31,** 2596 (1898) ; Doebner, O., *Ber*, **33**, 2140 (1900) ;

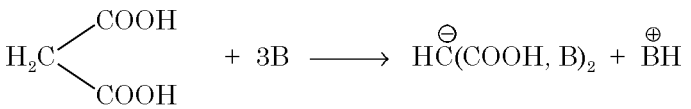
Tietze *et al. Synthesis,* 1185 (1994) ; Tietze and Beifuss, *Comp. Org. Syn.* **2**, 341–394, (1991) ; Prajapati, D. and J.S. Sandhu, *Chem. Letters*, 1945 (1992).

It is pertinent to mention here that Knoevenagel condensation is new invariably employed more widely and rationally to include *malonic acid analogues,* namely : diethyl monoethyl-malonate, ethyl cyanoacetate etc. Interestingly, a host of *heterocyclic secondary amines* may be used as **catalysts ;** and frequently the most effective is *piperidine* (hexahydropyridine) ; besides, a mixture of piperidine and **pyridine** or **pyridine** alone, is also often utilized for the said condensation reactions.

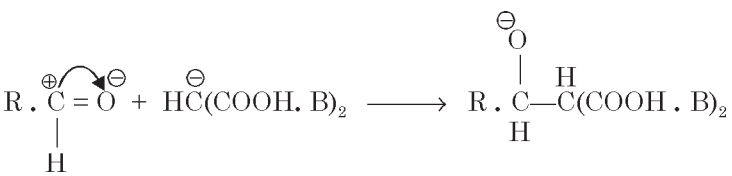
Interestingly, the specific role played by the heterocyclic secondary amine *i.e.,* the **base** is evidently primarily that of *a proton remover* from the **reactive methylene group.**

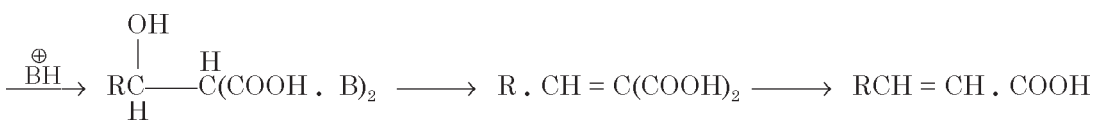
Explanation

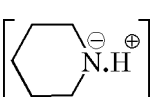
Reaction (*a*)



Reaction (*b*)





Let us assume that the '*base*' is represented by 'B', reaction (*a*) yields the carbanion, that subsequently combines with the positively charged carbon of the carbonyl function present in the *aldehyde* [reaction (*b*)]. Thus, the product regains a proton from the piperidinium ion 

; and finally loses a mole of water followed by mono-decarboxylation of the corresponding malonic acid residue thereby giving rise to the ultimate *acid*.

In short, the *Knoevenagel condensation* may be explicitely illustrated by the synthesis of sorbic acid as stated under :

4.5.2 Sorbic Acid

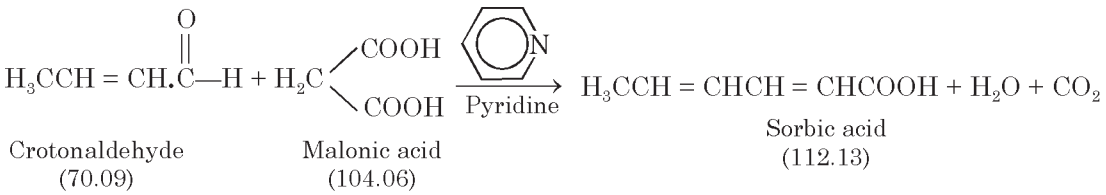
4.5.2.1 Chemical Structure

$$H_3C\,CH = CH\,CH = CH\,COOH$$

Sorbic Acid

4.5.2.2 Synonyms. 2,4-Hexadienoic acid ; 2-Propenylacrylic acid ;

4.5.2.3 Theory



Crotonaldehyde and malonic acid interacts in the presence of pyridine *i.e.,* a base, to yield sorbic acid together with one mole each of water and carbon dioxide. Pyridine acts as a catalyst in making the reaction proceed in the forward direction only.

4.5.2.4 Chemicals Required

Malonic acid : 5 g ; Pyridine : 5 ml ; Crotonaldehyde : 3.9 ml (3.4 g) ; Conc. Sulphuric acid : 2 – 3 ml ;

4.5.2.5 Procedure. The following steps are involved sequentially :

(1) Transfer 5 g malonic acid, 5 ml pyridine (freshly distilled) and 3.9 ml crotonaldehyde in a 100 ml round bottom flask fitted with a reflux condenser. Shake the contents thoroughly.

(2) Allow the contents of the flask to reflux very gently on a thermostatically controlled small heating mantle for a duration of 45-50 minutes. Cool the contents of the flask in ice-cold water to bring down the temperature between 5-6°C.

(3) Mix 2 ml concentrated H_2SO_4 very slowly and carefully to 4 ml water and chill the diluted acid in ice-bath to about 5-6°C.

(4) Add the diluted acid to the reaction mixture (2) in small lots at intervals with constant shaking so as to neutralize the base and liberate the desired sorbic acid.

(5) Sorbic acid readily separates as crystals from the resulting solution.

The yield of crude sorbic acid mp 131-132°C is 1.4 g.

4.5.2.6 Precautions

(1) Reflux of the reaction mixture in step-2 must be carried out very gently for 45-50 minutes.

(2) The acidification of the pre-cooled and completed reaction mixture should be carried out with chilled and diluted H_2SO_4 very carefully.

4.5.2.7 Recrystallization

Recrystallize the entire crude product from distilled water (~ 30 ml) and obtain the colourless crystals mp 133-134°C, weighing 1.25 g.

4.5.2.8 Theoretical yield/Practical yield

The theoretical yield of sorbic acid may be calculated from the equation under theory (section 4.5.2.3) as given below :

70.09 g of Crotonaldehyde on being reacted with Malonic acid

yields Sorbic Acid = 112.13 g

$\therefore$ 3.4 g of Crotonaldehyde shall yield Sorbic Acid $= \dfrac{112.13}{70.09} \times 3.4 = 5.44$ g

Hence, theoretical yield of Sorbic Acid = **5.44 g**

Reported Practical yield = 1.4 g

Therefore, Percentage Practical yield $= \dfrac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \dfrac{1.4}{5.44} \times 100 =$ **25.74.**

4.5.2.9 Physical Parameters. It is obtained as needles from water mp 134.5°C. It must be stored at temperatures below 40°C, bp 228°C (decomposes). It has pK (25°C) = 4.76.

Solubility Profile. It has solubility in water (30°C) 0.25% ; at 100°C 3.8% ; propylene glycol (20°C) 5.5% ; absolute ethanol or methanol 12.90% ; ethanol (20% v/v) 0.29% ; glacial acetic acid 11.5% ; acetone 9.2% ; benzene 2.3% ; CCl_4 1.3% ; cyclohexane 0.28% ; dioxane 11.0 % ; glycerol 0.31% ; isopropanol 8.4 % ; isopropyl ether 2.7% ; methyl acetate 6.1% and toluene 1.9%.

4.5.2.10. Uses

(1) It is abundantly used as a mold and yeast inhibitor in pharmaceutical preparations.

(2) It is also employed as a fungistatic agent for food products, especially cheeses .

4.5.2.11 Questions for *Viva-Voce*

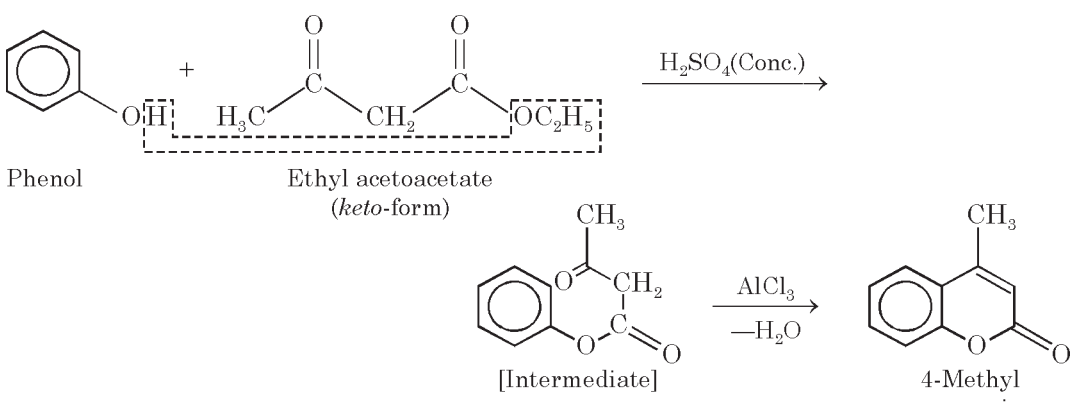
(1) How does pyridine act as a catalyst in Knoevenagel condensation ?

(2) Why is it necessary to chill the contents before starting the neutralization with dilute sulphuric acid.

(3) Explain Doebner modification to Knoevenal condensation.

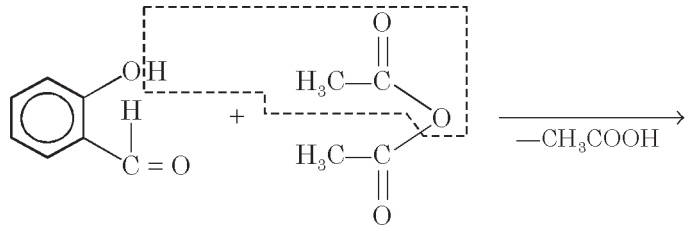
4.5.3 Pechman Condensation*

Pechman condensation essentially comprise of the synthesis of '*coumarins*' by the interaction of phenols with (3-keto esters particularly in the presence of *Lewis acid catalysts* as given below :

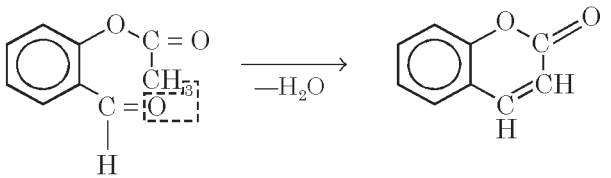


*Pechman, H.V., and Duisberg, C., *Ber.* **16**, 2119 (1883) ; Osborne, A.G., *Tetrahedron,* **37**, 2021 (1981) ; Kappe, T. and C. Mayer, *Synthesis,* 524 (1981).

Simple coumarin is usually prepared by heating salicylaldehyde with acetic anhydride in the presence of sodium acetate and treating the resulting product with conc. sulphuric acid as shown below :



Salicylaldehyde Acetic anhydride

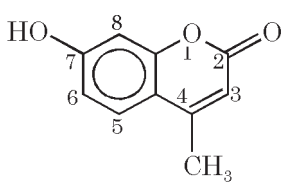


Intermediate Coumarin

Pechman condensation may also be exemplified by the synthesis of a 4-substituted coumarin, wherein a dihydroxy phenol (*e.g.*, resorcinol) may be condensed with ethyl acetoacetate under the influence of sulphuric acid to give rise to the formation of 7-hydroxy-4-methyl coumarin.

4.5.3.1 7-Hydroxy-4-methyl coumarin

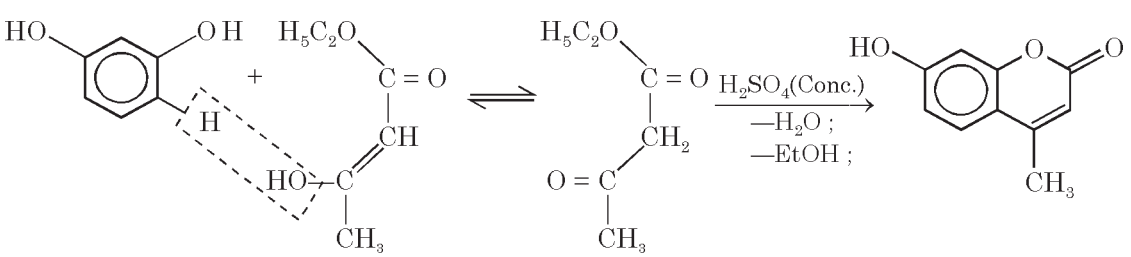
4.5.3.2 Chemical Structure



7-Hydroxy-4-methyl coumarin

4.5.3.3 Synonyms. 7-Hydroxy-4-methyl-2H-1-benzopyran-2-one ; Hymecromone ; Imecromone ; 7-Hydroxy-4-methyl-2-*oxo*-3-chromene ; 4-Methylumbelliferone ; β-Methylumbelliferone ;

4.5.3.4 Theory



Resorcinol (110.11) Ethylacetoacetate [*enol*-form] (130.14) Ethylacetoacetate [*keto*-form] 7-Hydroxy-4-methyl coumarin (176.17)

Resorcinol interacts with the *enol*-form of ethylacetoacetate in the presence of concentrated sulphuric acid to yield 7-hydroxy-4-methyl **coumarin** with the elimination of one mole each of ethanol and water.

4.5.3.5 Chemicals Required. Resorcinol : 4.6 g ; Ethyl acetoacetate : 5.6 g ; sulphuric acid (concentrated) : 18.75 ml ; NaOH (10% w/v)) : q.s ; and HCl (6 N) : q.s. ; Methylated Spirit : 30 ml ;

4.5.3.6 Procedure. The various steps involved are as stated under :

(1) Stir 18.75 ml of concentrated sulphuric acid mechanically in a wide-necked 100 ml flask provided with external ice-water chilling device until the temperature of the acid is about 4-5°C.

(2) Transfer 4.6 g of powdered resorcinol to 5.6 g (5.48 ml) of pure ethyl acetoacetate with constant stirring until a complete solution is achieved.

(3) Add this solution (2) very slowly into the sulphuric acid (1) in small lots at intervals taking care that the temperature of the reaction mixture should not rise above 10°C by any means. Continue further stirring for a duration of 30-40 of minutes with a view to complete the Pechman condensation reaction.

(4) Pour the contents of the flask in a very thin-stream directly onto 130 g of crushed ice with vigorous stirring with a glass rod, when the solid 7-hydroxy-4-methyl coumarin separates out readily.

(5) Filter off the crude 7-hydroxy-4-methyl coumarin on a Büchner funel under suction. Wash the product with a spray of cold water.

The yield of the crude product mp 192-193°C is 4.85 g.

4.5.3.7 Precautions

(1) The mixture of resorcinol and ethyl acetoacetate must be added to the previously cooled conc. H_2SO_4 with constant stirring very gradually so that the temperature of the reaction mixture should be maintained below 10°C.

(2) Further stirring for 30-40 minutes, after complete addition of reactants, is very important in order to allow the condensation to accomplish completely.

(3 Final production of the desired product is always achieved by pouring the reaction contents into crushed-ice with continuous vigorous stirring.

4.5.3.8 Recrystallization

The crude product is dissolved in cold aqueous solution of sodium hydroxide (10% w/v) ; and reprecipitated by adding dilute HCl carefully. The solid residue thus obtained is recrystallized from minimum quantity of methylated spirit, using powdered activated charcoal.

The yield of the recrystallized colourless product mp 194-195°C is 4.65 g.

4.5.3.9 Theoretical yield/Practical yield

The theoretical yield is calculated from the equation under theory (section 4.5.3.4) as stated below :

110.11 g of Resorcinol on interaction with 130.14 g of ethyl acetoacetate

shall yield 7-Hydroxy-4-methyl coumarin = 176.17 g

∴ 4.6 g of Resorcinol shall yield 7-Hydroxy-4-methyl coumarin

$$= \frac{176.17}{110.11} \times 4.6 = 7.36 \text{ g}$$

Hence, Theoretical yield of 7-Hydroxy-4-methyl coumarin = **7.36 g**

Reported Practical yield = 4.85 g

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$$= \frac{4.85}{7.36} \times 100 = \mathbf{65.89.}$$

4.5.3.10 Physical Parameters

It is obtained as crystals from alcohol mp 194-195°C. It has uv_{max} (methanol : 221, 251, 322.5 nm. It gives a distinct blue fluorescence in alcohol + water. It is soluble in methanol, glacial acetic acid ; slightly soluble in ether, chloroform ; and practically insoluble in cold water.

4.5.3.11 Uses

(1) It is invariably employed as cholerectic.*

(2) It is also used as antispasmodic.**

4.5.3.12 Questions for *Viva-Voce*

(1) Why does the '*enol*–Form' of ethyl acetoacetate react with resorcinol to yield 7-hydroxy-4-methyl coumarin ?

(2) Why is it important to add the admixture of resorcinol and ethyl acetoacetate onto conc. H_2SO_4 at a temperature below 5°C ?

4.6 DIAZOTIZATION AND COUPLING REACTIONS

[A] Diazotization Reactions. There exists a marked and pronounced difference between the *aliphatic amines* and the *primary aromatic amines* ; whereby the former reacts with **cold aqueous nitrous acid (HNO_2)** to give rise to the formation of the corresponding *primary alcohol* as the major product of reaction ; and the latter under identical experimental parameters exclusively results into the formation of *benzenediazonium chloride* (salt), sometimes also termed as *diazo-benzene chloride* as illustrated below :

(*a*) **Ethylamine (an aliphatic amine)**

$$\underset{\text{Ethylamine hydrochloride}}{H_5C_2—NH_2.HCl} + \underset{\text{Nitrous acid}}{HONO} \xrightarrow{0-5°C;} \underset{\text{Ethanol (a Pri-alcohol)}}{H_5C_2—OH} + N_2 + H_2O + HCl$$

*__Cholerectic :__ Any agent that increases excretion of bile by the liver.

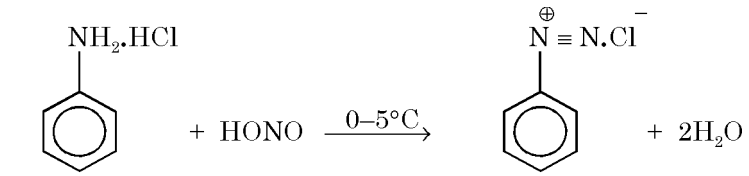
**__Antispasmodic :__ An agent that either prevents or relieves *spasm i.e.,* an involuntary sudden movement or muscular contraction that occurs as a result of some irritant or trauma.

In the above reaction HNO_2 (*i.e.,* nitrous acid) is generated by the interaction of sodium nitrite and dilute HCl as given below :

$$NaNO_2 + HCl \xrightarrow{0-5°C;} HNO_2 + NaCl$$

Nitrous acid is highly unstable and extremely volatile in nature ; therefore, the above reaction is invariably carried out between 0–5°C so that the HNO_2 generated instantly is fully utilized in the diazotization process. In this particular instance the two atoms of nitrogen escape out of the reaction mixture as nitrogen gas (N_2) leaving behind the primary aliphatic alcohol (*i.e.,* ethanol) in the reaction mixture.

(*b*) **Aniline (an aromatic primary amine)**

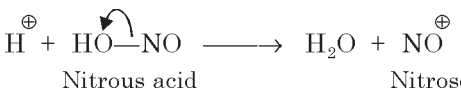


In the aforesaid reaction, aniline first-gets solubilized as its hydrochloride (*i.e.,* aniline hydrochloride) in aqueous medium ; thereafter, it undergoes diazotization with nitrous acid 0–5°C yielding the *benzene diazonium chloride* (salt) plus liberating *two* moles of water.

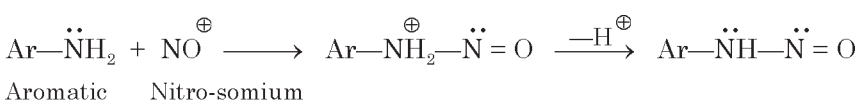
It is pertinent to mention here that the +ve charge usually resides on the N-atom *nearer to the aromatic ring* as shown above by virtue of the fact that the said N-atom is deficient in electrons (*i.e.,* N-atom has only four valancies out of five) ; and the second N–atom away from the benzene nucleus has all the three valancies duly satisfied. (**Note.** *N atom has two valancies 3 and 5).*

Mechanism. The formation of the *diazonium ion* by the interaction of **nitrous acid** and **aromatic primary amine** is usually accomplished by means of the following *four* sequential steps, namely :

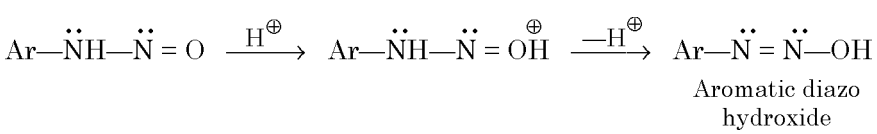
Step I.



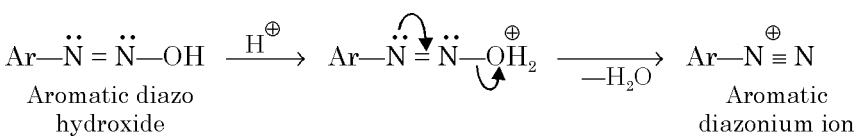
Step II.



Step III.



Step IV.



Explanation. In step-I, the nitrous acid reacts with the proton (H^+) from the mineral acid to yield nitrosonium ion.

In step-II, the resulting nitrosonium ion attacks the nucleophilic* nitrogen of the aromatic primary amine to form an adduct wherein the N atom nearer to the aromatic ring bears the +ve charge.

Further, loss of a proton yields the corresponding *aryl-imino-nitroso compound*.

In step-III, the aryl-imino-nitroso derivative takes up a proton in such a manner that the O-atom of the nitroso moiety gets protonated to give rise to a product bearing a +ve charge on the O-atom. Further, loss of a proton from the N atom adjacent to the aryl nucleus helps in shifting the double bond between terminal O and N atoms to N and N atoms thereby generating the *aromatic diazo hydroxide.*

In step-IV, the resulting aromatic diazo hydroxide retains a proton to give an intermediate wherein the terminal O atom bears a +ve charge. This intermediate encounters a prototropic shift, loses a mole of water and ultimately gives rise to the desired *aromatic diazonium ion.*

Having understood the various steps that are involved in the diazotization process, one may define it as—**'***A chemical interaction whereby an aromatic primary amine, having amino (–NH_2) function directly attached to the nucleus, upon treatment with nitrous acid in cold (0–5°C) yield diazonium salts***'**.

[B] Coupling Reactions. The **coupling reaction** is defined as—**'**An electrophilic substitution reaction involving the diazonium ion that eventually reacts at the position of greatest electron availability, *i.e.,* the position either *ortho*-or *para*-to the electron releasing amino or phenoxy functions**'**.

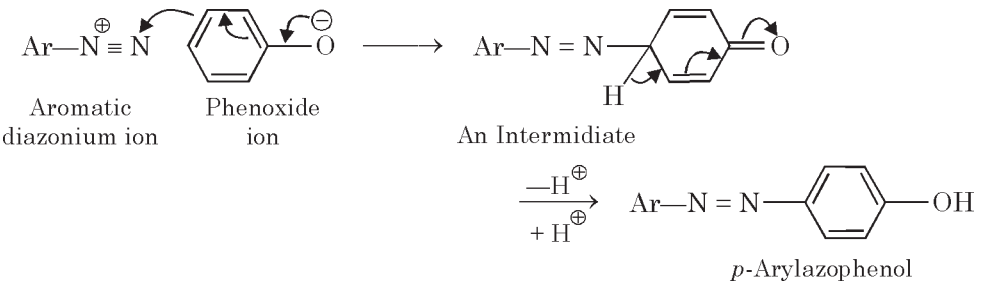
It has been observed that usually the **diazonium salt** couples at a vacant *para*-position, but in case this position is not available free, coupling invariably takes place at *ortho*-position. Furthermore, if none of these position is available free, *two* situations may arise, namely :

(*a*) Coupling reaction does not occur at all, and

(*b*) Functional moiety attached to *para*-position is knocked off entirely.

The *coupling reactions* may be exemplified as given below :

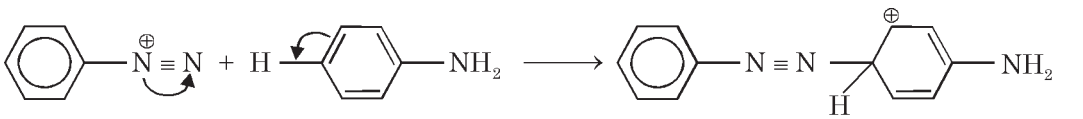
(*i*) **Coupling Reaction with Phenoxy Function :**

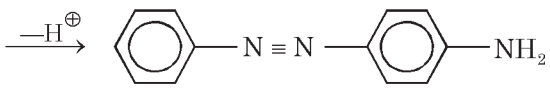


*__Nucleophilic :__ Having an attraction to nuclei.

The interaction between aromatic diazonium ion and the phenoxide ion undergo several prototropic shifts to give rise to a coupled intermediate product, which further affords intramolecular rearrangement to yield *para*-arylazophenol.

(*ii*) **Coupling Reaction with Amino Function :**





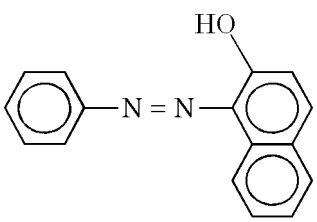
para-Aminoazobenzene

The reaction between phenyl diazonium ion and aniline results into the formation of an intermediate ion, which upon loss of a proton yields the coupled product *p*-aminoazobenzene.

Following are some typical examples where both diazotization and coupling reactions take place in succession to yield medicinal important compounds, such as : Phenyl-azo-β-naphthol ; 5-Diazouracil ; and Dimethyl-*p*-phenylenediamine.

4.6.1 Phenyl-azo-β-Naphthol

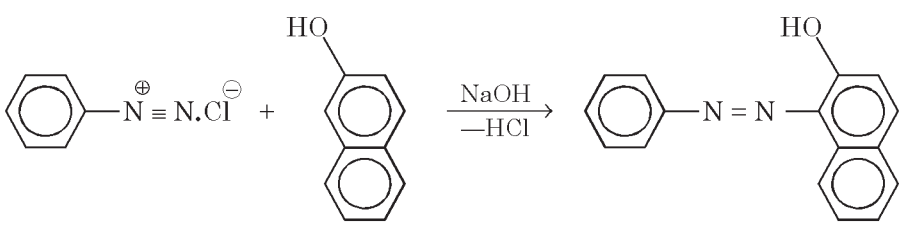
4.6.1.1 Chemical Structure



Phenyl-azo-β-naphthol

4.6.1.2 Synonyms. 1-Phenylazo-2-naphthol ; Benzene-azo-β-naphthol ;

4.6.1.3 Theory



Phenyl diazonium chloride (140.5) β-Naphthol (168) Phenyl-azo-β-naphthol (272)

Phenyl diazonium chloride is obtained first by the diazotization of aniline with nitrous acid as explained earlier, which on coupling with β-naphthol in the presence of NaOH solution yields the desired coupled product phenyl-azo-β-naphthol. A mole of HCl is eliminated which instantly reacts with NaOH from the medium to produce NaCl and H_2O. Importantly, both diazotization and coupling reactions are required to be carried out between 0-5°C.

4.6.1.4 Chemicals Required. Aniline (freshly distilled) : 4.0 g ; Hydrochloric acid conc. (12 N) : 12.8 ml ; β-Naphthol : 6.24 g ; Sodium hydroxide solution [10% (w/v)] : 40 ml ; Sodium nitrite (pure) : 3.2 g ;

4.6.1.5 Procedure. The various steps followed in the synthesis of phenyl-azo-β-naphthol are as state below :

(1) In a 250 ml beaker dissolve 4.0 g (3.92 ml ; 0.054 mol) of aniline in 12.8 ml conc. HCl and dilute it with 12.8 ml distilled water. Cool the contents of the beaker in an ice-bath with frequent stirring till it attains a temperature between 0-5°C. [One may observe that the freshly distilled oily aniline has completely dissolved in the aqueous medium as aniline hydrochloride.]

(2) Meanwhile, dissolve separately 3.2 g sodium nitrite in 15 ml water and chill the solution also in the same ice-bath (0–5°C).

(3) Diazotise the aniline solution (1) by the addition of sodium nitrite solution (2) in small lots (2 ml) at a time in intervals with vigorous stirring with a glass rod taking care that the temperature of the reaction mixture must not exceed beyond 5°C at any cost. (If required 10-15 g of crushed ice may be added into the reaction mixture to ensure proper chilling while diazotization is on).

(4) After the complete addition of sodium nitrite solution, it is required to test the reaction mixture for the presence of free nitrite by taking out a drop of it and immediately placing it on KI-starch paper that will distinctly turn blue in the presence of free nitrous acid. (It may be noted that by using good quality sodium nitrite and adding 10% excess than the theoretical value one may ascertain completion of diazotization reaction).

(5) Dissolve 6.24 g (0.054 mol) β-naphthol separately in a 250 ml beaker in 40 ml of sodium hydroxide solution, and cool the naphthol-solution in an ice-bath (0-5°C).

(6) Cautiously and slowly add the cold diazonium salt solution to the β-naphthol solution with vigorous constant stirring. Special care must be taken for not allowing the temperature of the reaction mixture rise beyond 5°C. If need be, crushed ice should be added in between while the coupling-reaction proceeds.

(7) A red colour develops and crystals of crude phenyl-azo-β-naphthol separate out. Allow the reaction mixture to stand for 30-40 minutes with stirring in between so as to complete the reaction. Filter the red product in a Büchner funnel using suction, and wash the same with ice-cold water. Drain the water by pressing with an inverted glass-stopper.

The yield of crude product mp 129-130°C is 9.5 g.

4.6.1.6 Precautions

(1) Aniline should be dissolved in aqueous HCl and cooled to 0-5°C.

(2) Good quality of $NaNO_2$ must be used ; and about 10% extra amount actually employed from the theoretical amount.

(3) The solution of β-naphthol in 10% (w/v) aqueous NaOH is made and chilled to 0-5°C.

(4) The coupling reaction is carried out in an ice-bath only because heat is generated during the course of reaction.

4.6.1.7 Recrystallization. The crude product (9.5 g) may be recrystallized from approximately 100-110 ml glacial acetic acid, and filter the deep red crystals with suction, wash with a little ethanol (or methylated spirit) to get rid of any residual glacial acetic acid. Finally dry the pure crystallized product upon filter paper. The yield of pure phenyl-azo-β-naphthol mp 130.5-131°C is 9.1 g.

4.6.1.8 Uses

(1) It is used as an important and useful stain for various pathological objects.

(2) It also finds its application as a biological stain.

4.6.1.9 Questions for *Viva/Voce*

(1) What is the importance of 'diazotization' reaction in medicinal chemistry ?

(2) How does diazotization and coupling reaction help to produce important medicinal dyes ?

(3) Why is it a must to carry out 'diazotization' at 0-5°C ?

(4) What is the major difference between diazotization of an aliphatic amine and an aromatic primary amine ?

(5) How does a diazotized entity gets coupled with an *amine* or a *phenoxy* function ?

(6) How would you test for the presence of HNO_2 in the completed reaction mixture ?

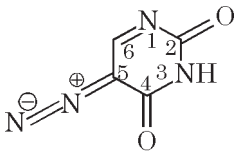
4.6.1.10 Special Note. In order to ascertain the presence of a slight excess of nitrous acid, *KI-starch paper* is invariably employed as an *external indicator ;* for this a drop of the solution from the reaction mixture being removed from time to time during the course of addition of the $NaNO_2$ solution, and subsequently dropped on to the paper. In a situation, when an excess of HNO_2 is present, I_2 gets liberated almost instantaneously which in turn renders the starch the distinct and familiar blue colouration, as given below :

$$2HONO + 2HCl + 2KI \longrightarrow 2NO + 2KCl + I_2 + 2H_2O$$

It is, however, pertinent to mention here that even long before the addition of the theoretical quantity of $NaNO_2$ is completed, the resulting solution from the reaction mixture usually gives a blue-colouration (which is most probably due to the atmospheric oxidation) within a few moments of being placed on the *KI-Starch paper.* Therefore, in case this indicator is to be used one may note and observe very critically than an excess of HNO_2 is NOT indicated to be present unless and until either an *instant* or *immediate* blue-colouration is accomplished when a drop of the solution is put in contact on the said indicator paper.

4.6.2 5-Diazouracil

4.6.2.1 Chemical Structure

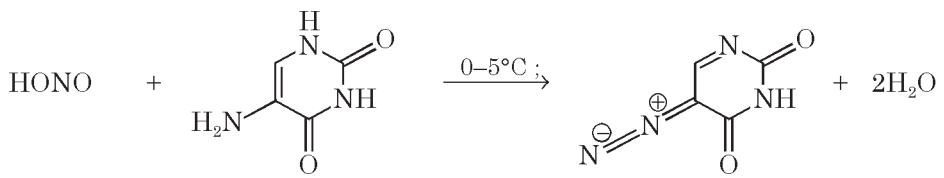


5-Diazouracil

4.6.2.2 Synonyms

2, 4-Dioxo-5-diazopyrimidine ; 5-Diazo-3, 4-dioxo-pyrimidine ; DU ; 5-Diazo-2, 4(1H, 3H)-pyrimidine-dione.

4.6.2.3 Theory



Nitrous acid	5-Amino uracil	5-Diazouracil
(47)	(127.09)	(138.09)

The 5-amino uracil interacts* with nitrous acid (generated from sodium nitrite and hydrochloric acid) at 0-5°C to produce one mole of 5-diazouracil and two moles of water.

4.6.2.4 Chemicals Required. 5-Amino uracil : 6.98 g ; Hydrochloric acid conc. (12 N) : 20 ml ; Sodium nitrite : 4.17 g.

4.6.2.5 Procedure. The following steps may be followed in a sequential manner.

(1) Dissolve 6.98 g (0.055 mol) of 5-amino-uracil in 20 ml of conc. HCl and 20 ml of water contained in a 150 ml conical flask. Cool the contents of the flask in an ice-bath to 0-5°C.

(2) Transfer 4.17 g of pure sodium nitrite into a 100 ml beaker or conical flask and dissolve it in 20 ml of distilled water. Chill the solution in an ice-bath below 5°C.

(3) Diazotize the 5-amino uracil (1) by the gradual addition of sodium nitrite solution (2) in small quantum (2 ml) at a time in intervals with vigorous stirring with a glass rod or on a magnetic stirrer. Ample care must be taken so that the temperature of the reaction mixture does not rise beyond 10°C.

[**Note :** *It is, sometimes advised to add even 10-15 g of crushed ice right into the reaction vessel while diatoziation reaction is on*.]

(4) After complete addition of sodium nitrite solution, it is necessary to test the reaction mixture for the presence of free nitrite as explained under section 4.6.1.6 (4) earlier.

The crude product, 5-diazouracil is obtained as crystals mp 195-196°C to the extent of 6.75 g.

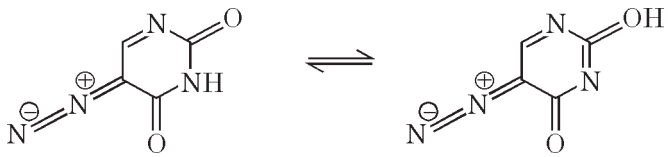
4.6.2.6 Precautions. All precautions that are essential for carrying out the diazotization reaction and described earlier may be adhered to strictly.

4.6.2.7 Recrystallization. The crude product may be recrystallized by dissolving it in minimum quantity of ice-cold distilled water and adding a few grammes of powdered activated

*Johnson *et al. Ber.* **64,** 2629 (1931).

charcoal so as to adsorb the undesired yellow or reddish colouration. The yield of the recrystallized product obtained as white crystals (mp 197–198°C) is 6.50 g.

4.6.2.8 Physical Parameters. It is obtained as stout white prisms, mp 198°C, that are usually found to be sensitive to light, air and temperature. It generally gives an acid reaction perhaps due to *keto-enol* tautomerism as shown below :



5-Diazouracil (*keto*-form) 5-Diazouracil (*enol*-form)

It shows IR spectrum : band at 4.57 μ. It gives rise to several well defined derivatives, such as : (*i*) Red monohydrate $C_4H_4N_4O_3$; (*ii*) Potassium salt obtained from (*i*), $KC_4H_3N_4O_3$, which being slightly soluble in water having almost neutral reaction ; and (*iii*) Alcoholates.

4.6.2.9 Uses

(1) It possesses significant activity against gram + ve and gram –ve bacteria *in-vivo.**

(2) It is found to be exhibiting cognizable interest in cancer research.

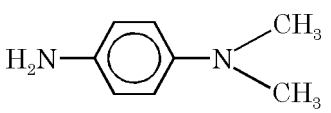
4.6.2.10 Questions for *Viva-Voce*

(1) How would you explain the acid reactions of 5-diazouracil that essentially contains four N-atoms of which two embedded in the ring and remaining two as the side-chain ?

(2) What are vital salient features of 5-diazouracil that make it a potential candidate in cancer research ?

4.6.3 Dimethyl-*p*-phenylenediamine

4.6.3.1 Chemical Structure



Dimethyl-*p*-phenylenediamine

4.6.3.2 Synonyms. N, N-Dimethyl-1, 4-benzenediamine ; *p*-Aminodimethylaniline ;

4.6.3.3 Synthesis. The synthesis of dimethyl-*p*-phenylenediamine can be accomplished in *two* steps as stated under :

Step I. Preparation of Methyl Orange, and

Step II. Preparation of Dimethyl-*p*-phenylenediamine.

These two aforesaid steps shall now be treated separately in the sections that follows :

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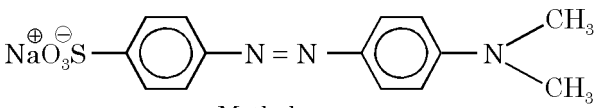
*Hunt, Pittillo, *Appl-Microbiol.* **16,** 1792 (1968).

Step I Preparation of Methyl Orange

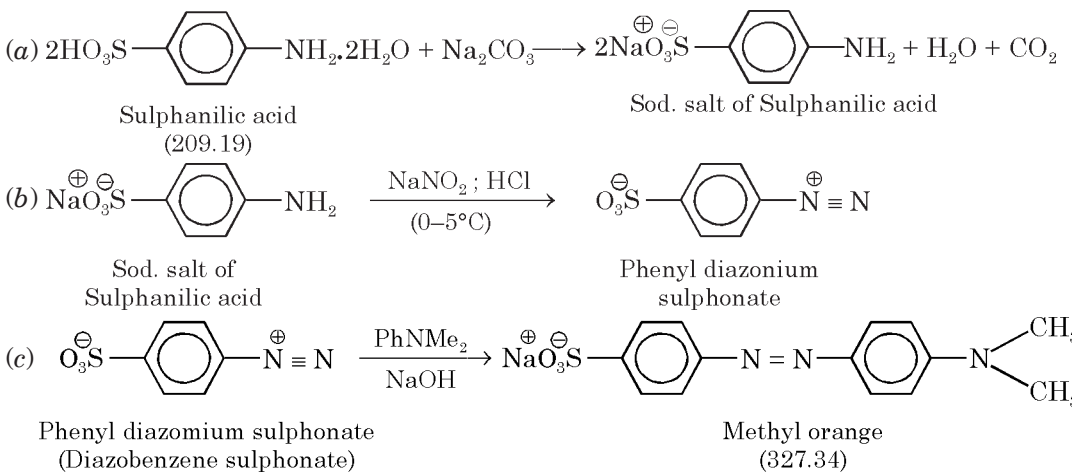
1. Chemical Structure



Methyl orange

2. Synonyms. 4-[[(4-Dimethylamino) phenyl]-azo] benzenesulphonic acid sodium salt ; Helianthine B ; CI Acid Orange 52 ; Orange III ; Gold Orange ; Tropaeolin D ;

3. Theory



Sulphanilic acid (209.19)

Sod. salt of Sulphanilic acid

Sod. salt of Sulphanilic acid

Phenyl diazonium sulphonate

Phenyl diazomium sulphonate (Diazobenzene sulphonate)

Methyl orange (327.34)

Interaction of sulphanilic acid and sodium carbonate gives the soluble sodium salt of sulphanilic acid, which upon diazotization yields the intermediate phenyl diazonium sulphonate. The resulting diazonium salt on reacting with dimethylaniline and sodium hydroxide produces the desired product methyl orange.

4. Chemicals Required. Sulphanilic acid dihydrate : 5.25 g ; Sodium carbonate (anhydrous) : 1.35 g ; Sodium nitrite : 1.9 g ; HCl (conc.) : 5.25 ml ; Dimethylaniline : 3.025 g : Glacial acetic acid : 1.5 ml ; Sodium hydroxide solution [20% (w/v)] : 17.5 ml ; and Sodium chloride : 5.0 g.

5. Procedure. The sequential steps involved in the synthesis of *Methyl Orange* are as stated below :

(1) Transfer 5.25 g (0.05 mol) of sulphanilic acid dihydrate into a 150 ml conical flask, 1.35 g (0.025 mol) of anhydrous sodium carbonate and 50 ml of distilled water, and warm the contents of the flask gently till complete dissolution is accomplished.

(2) Cool the resulting solution under a running tap by whirling the contents steadily till it attains 15°C, and add a solution of 1.9 g (0.059 mol) of sodium nitrite in about 5 ml of water.

(3) Gently pour the solution with constant stirring into a 500 ml beaker containing 5.25 ml of concentrated hydrochloric acid (12 N) and 40 g of crushed ice.

(4) After a duration of 15-20 minutes the test for the presence of free nitrous acid with potassium-iodide starch paper should be performed carefully.

(5) At this stage one may apparently observe the generation of the fine crystals of **diazobenzene sulphonate.**

[**Note :** *Do not filter the separated fine crystals of diazobenzene sulphonate at this particular stage because they would get dissolved in the course of the next stage of preparation.*]

(6) Separately dissolve 3.025 g (3.15 ml ; 0.05 mol) of pure dimethylaniline in 1.5 ml of glacial acetic acid ; and now add it in small lots at intervals with vigorous stirring to the suspension of diazotized sulphanilic acid.

(7) The resulting mixture is allowed to stand for 10 minutes ; the red or *acid form* of methyl orange shall separate out slowly.

(8) Add gradually and with constant stirring 17.5 ml of NaOH solution : the reaction mixture shall distinctly assume a uniform orange colouration on account of the separation of the sodium salt of methyl orange in the form of fine particles.

[**Note :** *Immediate and direct filtration of the resulting product is rather slow and cumbersome*.]

(9) Therefore, heat the above mixture to almost boiling with intermittent stirring. Thus, most of the product *i.e.,* methyl orange shall get dissolved. Add 5 g of solid NaCl (to help the subsequent separation of methyl orange) ; and warm upto 80-90°C until the salt has dissolved. Allow the resulting mixture to cool undisturbed for 20-30 minutes and subsequently in an ice-bath ; this gives rise to an appreciable easily filterable product.

(10) Filter off the desired crude methyl orange in Büchner funnel at the pump, while applying only gentle suction in order to avoid possible clogging the pores of the filter paper. The beaker may be subsequently rinsed with small quantity of saturated NaCl solution and drained well.

The yield of the crude product is about 6.4 g. It is, however, pertinent to state here that methyl orange, being a salt, has no definite and well-defined mp.

6. Precautions

(1) First of all sulphanilic acid needs to be converted to its corresponding sodium salt.

(2) Fine crystals of diazobenzene sulphonate are not usually separated from the reaction mixture, but the following step of reaction with dimethylaniline is carried out to obtain the final product.

(3) Heating of the mixture to boiling and then adding sodium chloride, cooling to 0-5°C finally gives rise to a reasonably feasible filterable product perhaps due to the agglomeration of fine particles of methyl orange.

7. Theoretical yield/Practical yield. The theoretical yield may be calculated from the equations (*a*) through (*c*) under theory (section 3) as given below :

209.19 g of Sulphanilic acid dihydrate, after diazotization, and on reacting

with dimethylaniline yield Methyl Orange = 327.34 g.

$\therefore$ 5.25 g of Sulphanilic acid shall yield Methyl Orange $= \frac{327.34}{209.19} \times 100 = 8.2$ g

Hence, Theoretical yield of Methyl Orange = **8.2 g**

Reported Practical yield = 6.4 g

Hence, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{6.4}{8.2} \times 100 =$ **78.04.**

8. Physical Parameters. Methyl orange is obtained as orange-yellow powder or crystalline scales which being soluble in 500 parts water, comparatively more soluble in hot water ; and almost insoluble in ethanol.

9. Uses

(1) It is mostly used as an indicator (0.1% aqueous solution) having *red colour* at pH 3.1 and *yellow colour* at pH 4.4.

(2) It is also used for estimating alkalinity of waters.

10. Questions for *Viva/Voce*

(1) Why is it important to carry out diazotization of sulphanilic acid between 0-5°C ?

(2) Why is it not advisable to filter off the fine crystals of diazobenzene sulphonate rather than carrying out the interaction with dimethylaniline in the reaction mixture itself ? Explain.

(3) How would your obtain the feasible and easily filterable methyl orange as a crude product ?

(4) Why methyl orange does not show a definite and well-defined mp ?

Step II. Preparation of Dimethyl-*p*-phenylenediamine

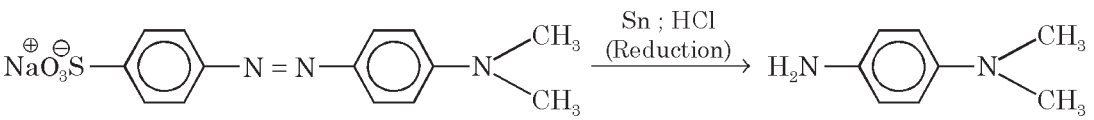
Dimethyl-*p*-phenylenediamine is usually obtained from methyl orange by *two* methods, namely :

(*a*) Reduction of methyl orange to *p-aminodimethylaniline,*

(*b*) Treatment with sodium dithionite.

1. Theory

(*a*) **Reduction with Tin/HCl**



Methyl orange Dimethyl-*p*-phenylenediamine

(*b*) **Treatment with Sodium dithionite**

$$\text{Methyl orange} \xrightarrow[\text{Sodium dithionite}]{Na_2S_2O_4} \text{Dimethyl-}p\text{-phenylenediamine}$$

Dimethyl-*para*-phenylenediamine is obtained from methyl orange either by reduction with tin metal and hydrochloric acid as shown in (*a*) above ; or by treatment with sodium dithionite ($Na_2S_2O_4$) as depicted in (*b*) above.

2. Method-I

(*i*) **Chemicals Required.** Methyl orange : 10 g ; Tin (II) chloride : 4 g ; Hydrochloric acid (concentrated) : 10 ml ; NaOH soln. [10% (w/v)] ; q.s ; Solvent ether : 100 ml ; Anhydrous potassium carbonate : 50 g ;

(*ii*) **Procedure**

(1) Dissolve 10 g of methyl orange in the minimum quantity of warm water ; and to this warm solution add a solution of 4 g of tin (II) chloride (*i.e.,* stanous chloride) in 10 ml of concentrated HCl (12 N) until complete decolourization is accomplished. One may affect gentle boiling, if necessary.

(2) Chill the resulting solution in an ice-bath ; when a crystalline precipitate comprising of sulphanilic acid and to some extent of *p*-aminodimethylaniline hydrochloride gets separated.

(3) At this stage addition of NaOH solution (10%) is affected carefully until the precipitate of tin hydroxide [$Sn(OH)_2$] redissolves ; and the *free-base* gets separated.

(4) The resulting cold solution is successively extracted with 3 to 4 times 25 ml portion of solvent ether, dry the combined ethereal extract with anhydrous K_2CO_3 and finally get rid of the ether by distillation under vacuum.

(5) The residual base comprising of dimethyl-*p*-phenylenediamine gets crystallised immediately, provided it is stirred with a glass rod. It has mp 40.5-41°C.

3. Method-II

(*i*) **Chemicals Required.** Methyl orange : 10 g ; Sodium dithionite : 5 g ; Solvent ether : 100 ml ; Anhydrous K_2CO_3 : 50 g.

(*ii*) **Procedure**

(1) Suspend 10 g of methyl orange in 2-3 ml of water ; and add a small amount of sodium dithionite ($Na_2S_2O_4$).

(2) Heat the mixture gently, and add small quantum of sodium dithionite unless and until the red colouration is discharged completely.

(3) Thus, the unwanted sulphanilic acid remains in the solution as sodium sulphanilate, while the desired product dimethyl-*para*-phenylene diamine may be extracted successively with solvent ether as described earlier in **Method-I.**

4. Physical Parameters. It is obtained as reddish-brown crystals having mp 53°C, bp 262°C, soluble in water, alcohol, chloroform and ether.

5. Uses

(1) Its dihydrochloride salt is extensively employed in microscopy.

(2) It is also used in carrying out the tests for acetone and uric acid in *urine samples.*

6. Questions for *Viva-Voce*

(1) What happens when methyl orange is subjected to reduction with metallic tin and hydrochloric acid ?

(2) How does sodium dithionate convert methyl orange to dimethyl-*p*-phenylenediamine ? Explain.

4.7 ORGANIC NAME REACTIONS (ONRs)

The Organic Name Reactions (ONRs) section categorically is intended to eater the professional medicinal chemist and students studying pharmaceutical chemistry by illustrating various *'organic chemical reactions'* that have extensively come to be acknowledged as genuine and valid, besides being referred to by specific name within the regimen and realm of **chemistry fraternity.**

In true sense, there are more than four hundred specific organic name reactions that have been adequately cited in literatures till date. These reactions do have their meaningful and purposeful academic interests to the pure organic chemists in particular and to the chemistry community in general.

However, it is thought worthwhile to include certain organic name reactions (ONRs) in the present context in this compendium by means of which medicinally useful compounds could be synthesized in the laboratory with a view to broaden the horizon of interest to the budding *'medicinal chemists'*.

A few selected organic name reactions (ONRs) are as given under :

(*i*) Bart Reaction,
(*ii*) Diels-Alder Reaction,
(*iii*) Friedel-Craft's Reaction,
(*iv*) Frie's Reaction,
(*v*) Grignard Reaction,
(*vi*) Hoesch Reaction,
(*vii*) Perkin Reaction,
(*viii*) Mannich Reaction,
(*ix*) Michael Reaction,
(*x*) Reimer-Tiemann Reaction.

4.7.1 Bart Reaction

Formation of *aromatic arsonic acids* are most readily and conveniently accomplished by the **Bart Reaction***, wherein a diazonium salt in an aqueous medium is poured into a solution of alkali arsenite (sodium arsenite) in an excess quantity of sodium carbonate. However, the presence of cupric salts (copper sulphate) or powdered silver or copper to the arsenite often achieves two important objectives : (*a*) induces a more regular effervescence due to the evolution of N_2 gas ; and (*b*) distinctly enhances the yield of the desired product.

It is pertinent to mention here that the success of the Bart Reaction when applied to nuclear-substituted anilines (*e.g., m*-substitued anilines) is invariably effected by the prevailing pH of the reaction medium. Scheller** (1992) and Doak*** *et al.* (1946) suggested certain modifications whereby the yields obtained from certain *m*-substituted anilines, which under the usual conditions of reactions are very low, could be enhanced considerably by carrying out

* Bart, H., **Gen. Pat.** 250, 264 (1910).

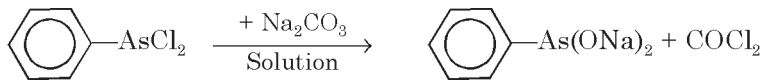
** Scheller, E., **Brit. Pat.** 261, 026 (1942).

*** Doak *et al. J. Am. Chem. Soc.,* **68,** 1987 (1946).

the diazotization in an ethanolic solution followed by reaction with arsenic trichloride ($AsCl_3$) in the presence of a CuCl or CuBr as a catalyst.

Extension of Bart Reaction. Interestingly, the *Bart Reaction* has been gainfully extended as stated below :

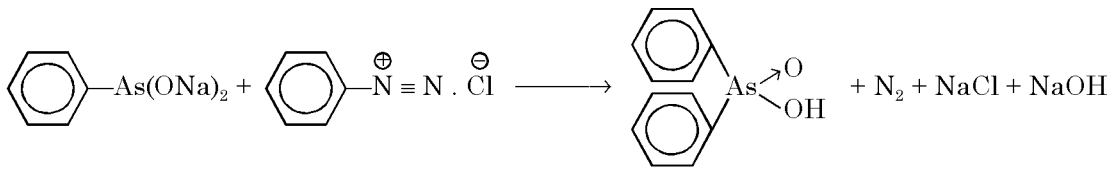
Example (*a*)



Dichloro-phenylarsine — Phenyl sodium arsenate — Phosgene

Dichlorophenylarsine when added to an excess of sodium carbonate solution it gives rise to the formation of phenyl sodium arsenate and phosgene.

Example (*b*)

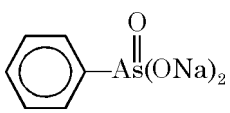


Phenyl sodium arsenate — Benzenediazonium chloride — Diphenylarsinic acid

Phenyl sodium arsenate on being treated with benzenediazonium chloride affords diphenylarsinic acid with the elimination of a mole each of nitrogen, sodium chloride and sodium hydroxide.

4.7.1.1 Phenylarsonic Acid

4.7.1.1.1 Chemical Structure

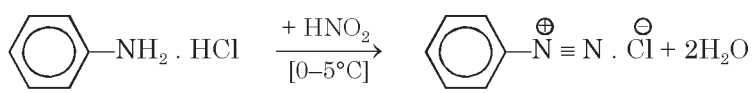


Phenylarsonic acid

4.7.1.1.2 Synonym. Benzenearsonic acid.

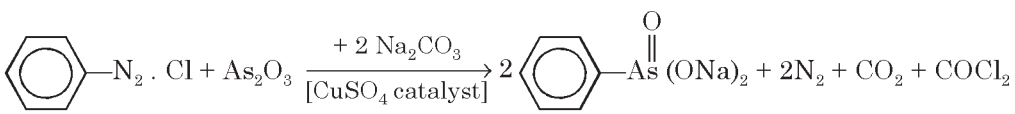
4.7.1.1.3 Theory

(*a*)



Aniline hydrochloride — Benzenediazonium chloride

(*b*)



Benzenediazonium chloride — Arsenious oxide — [HCl] — Phenylarsonic acid (Sod. salt)

Aniline hydrochloride first and foremost undergoes diazotization (see section 4.7) to give benzenediazonium chloride, which upon interaction with arsenious oxide **(Poison)** in the presence of sodium carbonate and cupric sulphate (catalyst) ultimately yields phenylarsonic acid.

4.7.1.1.4 Chemicals Required. Arsenious oxide : 6.75 g ; aniline : 5 ml (5 g); anhydrous sodium carbonate : 13.75 g ; crystalline copper sulphate : 0.25 g ; sodium nitrite (pure) : 3.9 g ; and hydrochloric acid (conc.) : 11.5 ml.

4.7.1.1.5 Procedure. The various steps involved are given below :

(1) Transfer in a sequential manner 6.75 g of arsenious oxide, 13.75 g of anhydrous sodium carbonate and 0.25 g of hydrated cupric sulphate to 45 ml of water in a 600 ml beaker. Heat the stirred mixture gently until an almost clear solution is accomplished. Immerse the resulting stirred clear solution in a freezing mixture, and cool the contents to 0–5°C.

(2) In a separate 150 ml beaker transfer 5 g (5 ml) of freshly distilled aniline to a mixture of 11.5 ml of concentrated HCl and 56 ml of water, and cool the mixture to 5°C in the ice-bath. Diazotize this solution in the usual manner by the gradual addition of a solution of 3.9 g of sodium nitrite in 12.5 ml of water. Allow the temperature of the resulting mixture to rise to 10–12°C for about 10-15 minutes so as to ensure complete diazotization.

(3) Add the solution of diazonium chloride (2) in small lots at intervals from a dropping funnel right into the vigorously-stirred arsenite solution (1), maintaining the temperature of the latter at 5–7°C.

Note : *At this particular instance most commonly frothing is caused by the brisk evolution of N_2–gas that would probably be dispersed by constant stirring. In case, the frothing still persists, the addition of 2-3 ml of solvent ether, preferably in a fine-jet from a wash-bottle, may cause it to subside promptly.*

(4) Once the diazotization is complete, remove the external cooling and continue the stirring for 40-45 minutes. Filter the resulting solution and evaporate it (by direct boiling) to about 35 ml. Add concentrated HCl (about 8.5 ml) carefully to the hot solution until effervescence stops completely (neutralization of excess of Na_2CO_3) ; and the separation of gummy material is more or less nears completion.

(5) Filter the warm solution, and chill the filtrate in ice-water for 5-6 minutes. Now, add conc. HCl (2.5 ml) *very slowly* with constant stirring until the resulting solution is *just* acidic to Congo Red. **[To achieve this use Congo Red Paper with external spolting with a glass rod.]**

(6) Phenylarsonic acid normally gets separated from the cold stirred solution within a span of 15-20 minutes.

Note : *In case separation does not occur, perhaps due to the addition of excess acid, add a few drops of dilute aqueous NaOH (1% w/v) and again bring the solution very carefully to the desired pH.*
The yield of the crude product (mp 153–156°C) is 6.5 g.

4.7.1.1.6 Precautions

(1) Diazotization should be carried out very cautiously and carefully.

(2) Interaction between the arsenite and the diazonium chloride must be carried out slowly at 5–7°C.

(3) Frothing may be controlled by spraying solvent ether (2-3 ml) to the reaction mixture.

(4) Neutralization of the final reaction mixture must be done very carefully with conc. HCl using Congo Red Paper ; and external spolting with a glass rod.

4.7.1.1.7 Recrystallization. The crude precipitated phenylarsonic acid may be recrystallized by either of the following methods, namely :

Method-I. Dissolve 5 g of the crude product in a minimum quantity of cold aqueous sodium carbonate solution (10% w/v) ; a second relatively small crop of the gummy impurity thus obtained may be discarded. Add 0.5–1.0 g of powdered animal charcoal, stir for a few minutes and filter at the pump. Acidify the filtrate with conc. HCl carefully to Congo Red Paper. The acid is precipitated on chilling, filter at the pump, wash with a small amount of cold water, drain well and finally dry it in a vacuum desiccator. The yield of the recrystallized product is 4.25 g having mp 152.5–154.5°C.

Method-II. Recrystallize 5 g of the crude product from a minimum volume of boiling water and adding 0.5–1 g of powdered activated charcoal. Filter through a pre-heated Büchner funnel and chill the filtrate to 0–5°C. Filter off the separated acid and wash, drain and dry as described in Method-I above. The yeild of the recrystallized product is 4.25 g and exhibits *two ranges* of mp as given below :

(*i*) Heated from room temperature : 152–155°C ;

(*ii*) Immersed in a heating-bath (140°C) : 155–156°C.

4.7.1.1.8 Theoretical Yield/Practical Yield

The theoretical yield is calculated from the equation under theory section 4.7.1.3 as given below :

93 g of Aniline *via* benzenediazonium chloride and arsenious oxide

yields Phenylarsonic acid = 202.24 g

$\therefore$ 5 g of Aniline shall yield Phenylarsonic acid $= \frac{202.04}{93} \times 5 = 10.86$ g

Hence, Theoretical yeild of Phenylarsonic acid = **10.86 g**

Reported Practical yield = 6.5 g

Therefore, Percentage Practical Yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{6.5}{10.86} \times 100 =$ **59.85**

4.7.1.1.9 Physical Parameters. Phenylarsonic acid is obtained as a crystalline powder having mp 158–162°C with decomposition. It is found to be soluble in 40 parts of water ; 50 parts of ethanol ; and almost insoluble in chloroform.

4.7.1.1.10 Uses. The first compound of this type to be introduced into medicine was *atoxyl* (*i.e.,* sodium salt of 4-aminophenylarsonic acid) for the treatment of protozoal diseases, such as : syphillis, relapsing fever, sleeping sickness and amoebic dysentery.

4.7.1.1.11 Questions for *Viva-Voce*

(1) Why is it absolutely necessary to carry out the diazolization strictly between 0–5°C.

(2) How would you accomplish the neutralization of the final reaction to obtain phenylarsonic acid ? Explain.

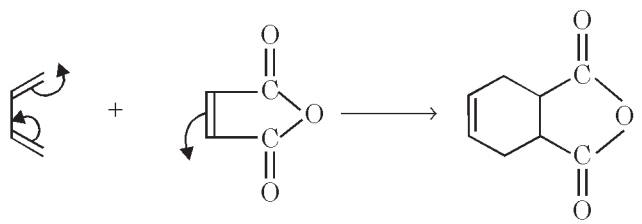
(3) What are the two methods for recrystallization of the crude product ? Explain.

4.7.2 Diels-Alder Reaction

Cycloaddition reactions invariably represent an important route to *'alicyclic compound'*. However, the most versatile and predominant for 6-membered rings is the **Diels-Alder Reaction.** It is pertinent to mention here that it is both *regioselective* and *stereospecific*, and hence affords considerable applications.

The **Diels-Alder Reaction** essentially consists in the direct combination of a compound possessing a *conjugated diene system* with a reagent that contains either a double-bond or a triple-bond, usually activated by conjugation with additional multiply-bonded systems, such as : cyano, carbonyl, nitro, phenyl functions. It ultimately adds on to the 1, 4-positions of a conjugated diene system (*e.g.,* buta-1, 3-diene) with the formation of a 6-membered ring. Importantly, the ethylenic (double-bond) or acetylenic (tripple-bond) compound is normally termed as the **dienophile,** the second reactant as the **diene** ; and the final desired product as the **adduct.** A few typical examples of such reagents are, namely : maleic anhydride, *para*-benzoquinone, acetaldehyde and acetylene dicarboxylic esters.

Examples :



Butadiene (DIENE) | Maleic anhydride (DIENOPHILE) | Adduct of butadiene and maleic anhydride (ADDUCT)

The above reaction is exemplified by the union of butadiene with maleic anhydride to form an adduct of butadiene and maleic anhydride.

Mechanism. The **Diels-Alder Reaction** is regarded as a concerted reaction in which four π-electrons from the *diene* and two π-electrons from the *dienophile* participate in the transition state to form the **adduct.** The Woodward-Hoffmann Rules* provide a theoretical framework for these reactions. It has been advocated that those reactions are permissible thermally that essentially possess $4n + 2$ pericyclic electrons *i.e.,* 6, 10, 14 etc. Thus, the Diels-Alder reaction is an example where $n = 1$, *i.e.,* (4 + 2) π-electrons.

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* Woodward, R.B., and R. Hoffmann : *The Conservation of Orbital Symmetry,* Academic Press, New York (1970).

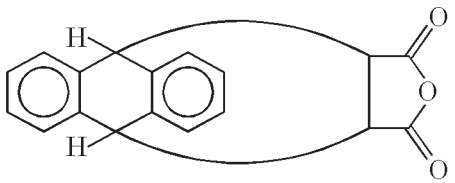
Utilities. The Diels-Alder Reaction has two great utilities, namely :

(*a*) For diagnosing the presence of a conjugated diene grouping, and

(*b*) For synthetic purposes in the preparation of the cyclic systems.

4.7.2.1 9, 10-Dihydroanthracene-9, 10-endo-ab-succinic anhydride

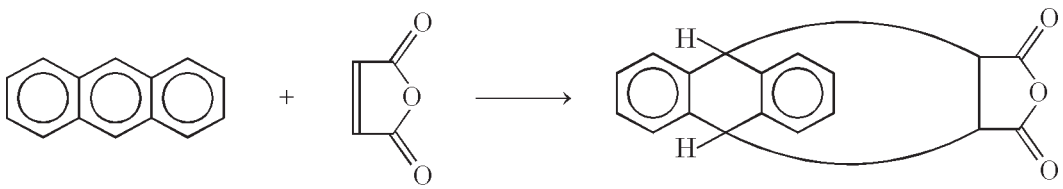
Chemical Structure



9, 10-Dihydroanthracene-9,10-*endo*-αβ-succinic anhydride

Synonyms. Adduct of anthracene and malic anhydride

Theory



Anthracene (178.23) + Maleic anhydride (98.06) → 9,10-Dihydroanthracene-9,10 -*endo*-αβ-succinic anhydride (276)

In this particular instance the Diels-Alder reaction is vividly exemplified by the union of anthracene with maleic anhydride to give rise to the formation of 9, 10-dihydroanthracene-9,10-*endo*-αβ-succinic anhydride. However, it may be observed that by virtue of this reaction both the outer rings of the *anthracene nucleus* have become truly aromatic in character.

Chemicals Required. Anthracene : 4.0 g ; Maleic anhydride : 2.2 g ; Xylene (or Xylol) : 100 ml ; Animal Charcoal : 2 g.

Procedure. The following steps may be followed in a sequential manner :

(1) Transfer 4 g anthracene, 2.2 g maleic anhydride and 50 ml absolutely dry xylene in a 150 ml round bottom flask fitted with a reflux condenser.

(2) Boil the reaction mixture for 30 minutes under reflux and then allow the contents of the flask to cool down to ambient temperature.

(3) In case, the reaction mixture appears to be coloured, add 1 g of finely powdered activated charcoal and again reflux for 5–7 minutes.

(4) Filter the hot solution through a Büchner funnel with suction, and on subsequent cooling the filtrate colourless crystals of adduct are obtained.

The yield of the crude product dried under vacuum desiccator is 4.3 g having mp 256–258°C.

Precautions

(1) Maleic anhydride should be of good quality so as to obtain the adduct in its purest form.

(2) Xylene must be free from moisture.

(3) Reflux must be carried out gently for the stipulated period only.

(4) Activated charcoal must be powdered so as to increase its surface area for its better effectiveness.

Recrystallization. Recrystallize the crude product from about 50 ml of xylene by boiling it ; and filtering the solution through a small preheated funnel, because the solute rapidly crystallises as the solution begins to cool. Place the recrystallised product in a vacuum desiccator, preferably over fresh paraffin-wax shavings to absorb traces of xylene. The recrystallized addition product is obtained as colourless crystals, mp 262–263°C, with a yield of 4.1 g.

Theoretical Yield/Practical Yield. The theoretical yield is calculated from the equation under theory (section 4.7.2.3) as given under :

178.23 g of Anthracene on reacting with 98.06 g of Maleic anhydride yields the adduct = 276 g

$\therefore$ 4.0 g of Anthracene shall yield Adduct $= \dfrac{276}{178.23} \times 4 = 6.19$ g

Hence, Theoretical yield of Adduct = **6.19 g**

Reported Practical Yield = 4.30 g

Therefore, Percentage Practical Yield $= \dfrac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \dfrac{4.30}{6.19} \times 100 =$ **69.47**

Uses. A marked improvement in the low temperature flow property of a fuel oil having a bp 120–150°C by adding a novel compound prepared by reacting *pri-, sec-* or *tert-* aliphatic amine containing alkyl group of 1–30 C-atoms with 9,10-dihydroanthracene-9,10-*endo*-αβ-succinic anhydride (or acid) there of together with a polymer having ethylene structure present relates compound temperature fluidity middle distillate composition petroleum fuel.

Questions for *Viva-Voce*

(1) What is the underlying mechanism of Diels-Alder reaction ?

(2) What are the two major utilities of Diels-Alder reaction ?

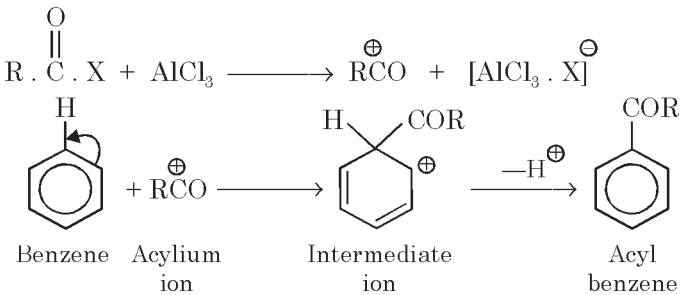
(3) Diels-Alder reaction is both regioselective and *stereospecific.* Explain.

4.7.3 Friedel-Crafts Reaction

The acyl or alkyl halides react with aromatic hydrocarbons or their derivatives in the presence of *anhydrous* aluminium chloride to produce their acyl or alkyl derivatives respectively. The ensuing reaction is usually termed as **Friedel-Crafts Reaction**, which is essentially regarded as an *electrophilic substitution reaction.*

Examples :

(*a*) *Acylation proceeds as follows :*



Acyl halide reacts with aluminium chloride to give rise to the acylium ion together with an anion *i.e.,* $AlCl_3$.X. The aromatic hydrocarbon interacts with the generated acylium ion to yield the corresponding intermediate ion, which subsequently loses a proton to result into the formation of acyl benzene.

Salient Features of Acylation. Following are the salient features of Friedel-Crafts acylation, namely :

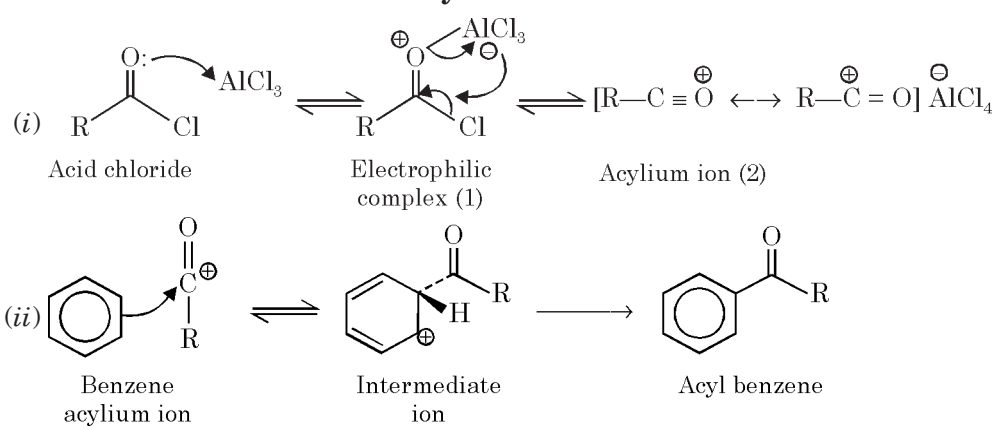
(1) At least one molar equivalent of $AlCl_3$ is necessary for each carbonyl moiety present in the acylating agent. It is because $AlCl_3$ is capable of forming rather stable complexes with the carbonyl moiety.

Note. *Complexation essentially requires an equivalent amount of* ***metal halide*** *; and, therefore, a slight excess over and above this quantity is normally employed so as to ensure that the* ***free reagent*** *should be present to act as the catalyst. Hence, 1.2 and 2.2 molar equivalents of* $AlCl_3$ *are generally employed for acid chlorides and acid anhydrides respectively.*

(2) In actual practice, an excess of *benzene* or of *toluene* is used as a solvent (when either of these solvents constitutes one of the reactants), otherwise nitrobenzene or carbon disulphide is normally employed.

(3) Friedel-Crafts acylation is usually free of two characteristic features that invariably make the alkylation reaction duly complicated, such as : (*a*) rearrangements ; and (*b*) polysubstitution.

Mechanism of Friedel-Crafts Acylation Reaction :



The Equation (*i*) above clearly depicts the manner in which an acid chloride interacts with aluminium chloride to form an electrophilic complex (1). Further, it most probably involves the acylium ion (2) as the reactive electrophilic species, although an electrophilic complex (1) between the acid chloride and the aluminium chloride may also be engaged.

The Equation (*ii*) above illustrates how the acylium ion interacts with benzene to form an intermediate ion *via* a reversible reaction, which ultimately results in the formation of acyl benzene.

Advantages of Aliphatic Carboxylic Acid Anhydrides. The use of aliphatic carboxylic acid anhydrides instead of the corresponding acid chlorides offers multifarious advantages as stated under :

(1) The anhydrides are usually obtained commercially in a state of high degree of purity quite easily and conveniently (*e.g.,* acetic, propanoic, butanoic and succinic anhydrides).

(2) Handling of corrosive and disagreeable chlorides may be avoided completely.

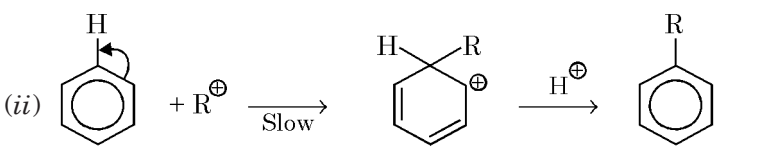
(3) Noticeable absence of appreciable amounts of resinous substances and by-products.

(4) Reaction generally proceeds smoothly with invariably a good yield.

(*b*) **Alkylation proceeds as follows :**

(*i*) $RX + AlCl_3 \longrightarrow R^{\oplus} + [AlCl_3X]^{\ominus}$

(*ii*)



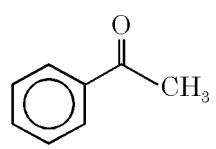
Benzene — Intermediate ion — Alkyl benzene

Equation (*i*) shows the interaction between an alkyl halide and aluminium chloride to yield the alkyl ion and the aluminium chloride-halide anion. In Equation (*ii*) the alkyl ion reacts with benzene to form the intermediate ion in a rather slow mode, which subsequently loses a proton to form the desired alkyl benzene.

Other Catalysts used in Friedel-Crafts Reaction. In addition to aluminium chloride there are a number of other catalysts that are used frequently, such as : Ferric chloride [$FeCl_3$] ; Boron trifluoride [BF_3] ; Zinc chloride [$ZnCl_2$] etc.

4.7.3.1 Acetophenone

4.7.3.1.1 Chemical Structure



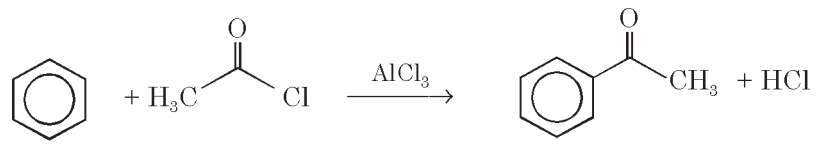
Acetophenone

4.7.3.1.2 Synonyms. 1-Phenylethanone ; Phenyl methyl ketone ; Hypnone ; Acetylbenzene ;

Acetophanone may be prepared by the following *two* methods :

Method-I. From Acetyl chloride

1. Theory



Benzene (78) — Acetyl chloride (78.5) — Acetophenone (120.15)

The interaction of benzene with acetyl chloride in the presence of anhydrous aluminium chloride as a catalyst gives rise to the formation of acetophenone with the elimination of one mole of hydrochloric acid.

2. Chemicals Required. Benzene (AR–Grade) : 25 ml ; Pure anhydrous aluminium chloride : 10 g ; Acetyl chloride (redistilled) : 7 ml.

3. Procedure. The various steps involved in the synthesis are as enumerated below :

(1) Transfer 10 g anhydrous aluminium chloride and 25 ml benzene in a 250 ml three-necked round bottom flask duly fitted with a reflux condenser, dropping funnel and the third neck is stoppered. Allow the contents of the flask to cool in a water-bath.

(2) Pour 7 ml of acetyl chloride into the dropping funnel carefully which is fitted to the three-necked flask. Start adding the acetyl chloride dropwise with constant gentle shaking into the reaction flask.

(3) Once the entire acetyl chloride has been added, heat the flask on an electric water bath precisely at 50 ± 2°C for a duration of 60 minutes.

(4) Allow the reaction mixture to cool down to room temperature by swirling its contents under a running cold tap-water. Immediately transfer the reaction mixture into 75 ml chilled water in a 150 ml conical flask previously containing a few pieces of ice chips when a dark coloured oil starts floating on the surface.

(5) Stopper the 150 ml flask tightly and shake the contents vigorously. In case, any solid particle commences to separate at this stage, add a few drops of conc. HCl to dissolve the same.

(6) Transfer the mixture to a separating funnel and discard the unwanted lower aqueous layer. Carry out the washing of the benzene layer initially with dilute NaOH (2% w/v) solution and then followed with water several times. Dry the benzene layer over anhydrous fused $CaCl_2$.

(7) Transfer the residual liquid mixture to a quick-fit distillation assembly ; and proceed with the distillation on an electric heating mantle carefully. Benzene shall be distilled as the first fraction around 80°C. Continue the process of distillation by elevating the temperature of the heating mantle gradually when acetophenone gets collected between 195–202°C. The yield of pure acetophenone bp 201°C, is 6.6 g.

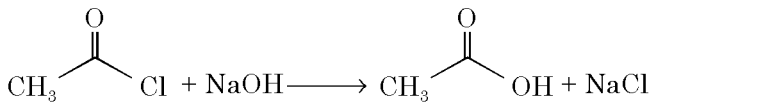
4. Precautions

(1) All the reactants *e.g.,* benzene, aluminium chloride and acetyl chloride must be of highest purity so as to obtain better yeild and pure product.

(2) The addition of acetyl chloride into the reaction mixture of benzene and $AlCl_3$ should be extremely gradual with constant swirling of the contents.

(3) Completion of reaction must be accomplished by heating the reaction mixture for 1 hr.

(4) The washing of the reaction mixture with aqueous dilute NaOH solution is *immensely important* so as to get rid of the unreacted acetyl chloride as acetic acid and NaCl, both being water-soluble, as shown below :



Acetyl chloride Acetic acid Sodium chloride

(5) The follow up washing with water shall remove the acetic acid and NaCl.

(6) The bp of *benzene* and *acetophenone* has a vast difference, and hence, both may be collected separately with great convenience.

5. Theoretical Yield/Practical Yield. The theoretical yield is calculated from the equation under theory (section 1) as given below :

78 g of Benzene on reacting with 78.5 g of acetyl chloride

yields Acetophenone = 120.15 g

$\therefore$ 21.97 g of Benzene shall yield Acetophenone $= \dfrac{120.15}{78} \times 100 = 33.8$ g

Hence, Theoretical yield of Acetophenon = **33.8 g**

Reported Practical Yield = 6.6 g

Therefore, Percentage Practical Yield $= \dfrac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \dfrac{6.6}{33.8} \times 100 =$ **19.5**

6. Physical Parameters. It is obtained as a liquid, but forms laminar crystals at low temperature having mp 20.5°C. It has physical parameters as : d_{15}^{15} 1.033 ; bp 202°C ; and n_{D}^{20} 1.533 g. Its flash point when determined by closed cup method is found to be 105°C. It is slightly soluble in water ; and freely soluble in alcohol, chloroform, glycerol, fatty oils and ether. Its solution in concentrated H_2SO_4 gives a distinct orange colouration.

7. Uses

(1) It is found to exert a hypnotic action.

(2) It is also used in perfumery to impart an orange-blossom-like odour.

(3) It is generally employed as a photosensitizer.

(4) It acts as a catalyst for the polymerization of olefins.

(5) It serves extensively as a flavoring agent for almond, roasted beef, cassie acacia, farnesiana, castoreum, and cherry.

(6) It is invariably employed as a fragrance for tobacco and beverages.

8. Questions for *Viva-Voce*

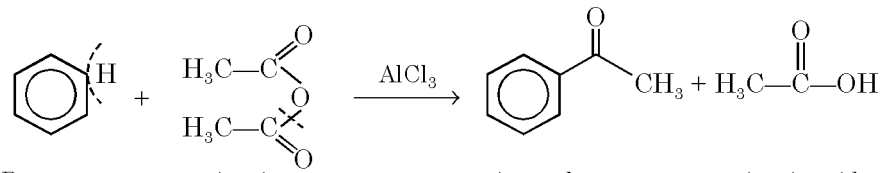
(1) Why is it absolutely necessary to add acetyl chloride into the reaction mixture containing benzene and $AlCl_3$ very slowly ?

(2) Why is it mandatory to wash the benzene layer first with dilute NaOH solution followed by water ?

(3) What are the two chemical substances that are obtained by the distillation of the final residual product ?

Method–II. From Acetic Anhydride

1. Theory



Benzene (78) | Acetic anhydride (102.09) | Acetophenone (120.15) | Acetic acid

The interaction of benzene with acetic anhydride in the presence of aluminium chloride (anhydrous) as a catalyst cleaves the anhydride to abstract an active hydrogen atom from benzene to yield acetophenone and a mole of acetic acid.

2. Chemicals Required. Benzene (AR) : 30 ml ; Anhydrous Aluminium chloride : 20 g ; Acetic anhydride : 6 ml ; Solvent Ether : 20 ml ; Hydrochloric Acid (6 N) : 75 ml ; NaOH Solution [20% (w/v)] 13.5 ml.

3. Procedure

(1) Add 20 g of anhydrous aluminium chloride and 30 ml of benzene in a 250 ml three-necked round bottom reaction flask.

(2) To this add 6 ml of acetic anhydride from the dropping funnel very slowly in small lots at intervals with constant stirring.

(3) Once the total amount of acetic anhydride has been added reflux the contents of the flask on an electric water-bath for a duration of 30 minutes.

(4) Allow the contents of the flask to attain room temperature and pour the reaction mixture into 30 ml of HCl (6N) taken in a 250 ml beaker having a few pieces of crushed ice. Stir the solution vigorously with a glass rod untill all the aluminium chloride has almost dissolved.

(5) Transfer the reaction mixture to a separating funnel and add to it 10 ml of ether. Shake and separate the benzene layer. To the aqueous layer and the remaining 10 ml portion of ether, shake and separate. Mix this *ethereal layer* with *benzene layer*.

(6) Wash the combination of benzene and ether layer first with 13.5 ml of NaOH solution and subsequently with water several times.

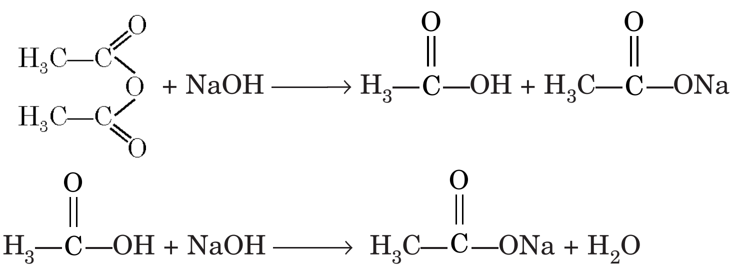
(7) Dry the washed benzene layer over anhydrous fused $CaCl_2$ in a dessicator ; and distil as described in Method-I. First of all ether will be distilled at 36°C, followed by benzene at 80°C ; and finally pure acetophenone may be obtained at 200–202°C with a yield of 6.2 g.

4. Precautions

(1) Pure grades of benzene and $AlCl_3$ are to be used in this synthesis.

(2) Addition of acetic anhydride must be carried out very gradually at intervals with constant stirring.

(3) Washing of the reaction mixture, after completion of the reaction, should be done with requisite quantity to aqueous NaOH solution to get rid of the unreacted acetic anhydride as given below :



Summararily, all the unreacted acetic anhydride shall be converted to water-soluble sodium acetate.

(4) The distillation must be carried out with a quick-fit assembly to collect the three fractions at 36°C (ether), 80°C (benzene), and 201°C (acetophenone).

5. Theoretical Yield/Practical Yield. The theoretical yield is calculated from the equation under theory (section 1) as stated under :

78 g of Benzene on reacting with 102.09 g of Acetic anhydride

shall yield Acetophenone = 120.15 g

∴ 26.36 g of Benzene shall yield Acetophenone $= \frac{120.15}{78} \times 26.36 = 40.60$ g

Hence, Theoretical yield of Acetophenone = **40.60 g**

Reported Practical Yield = 6.2 g

Therefore, Percentage Practical Yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{6.2}{40.6} \times 100 = \mathbf{15.27}$

The *Physical Parameters* and the **Uses** of acetophenone are same as discussed under Method-I above.

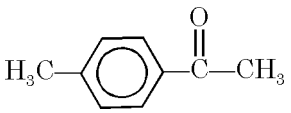
6. Questions for *Viva-Voce*

(1) Why is it advisable to add acetic anhydride into the reaction mixture containing benzene plus $AlCl_3$ very slowly with constant stirring ?

(2) Why is it recommended to wash the benzene layer first with dilute NaOH solution followed by water ?

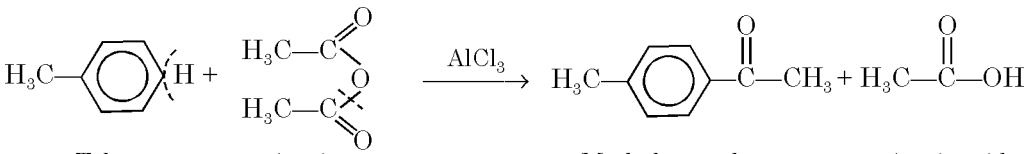
4.7.3.2 *p*-Methylacetophenone

4.7.3.2.1 Chemical Structure



p-Methylacetophenone

4.7.3.2.2 Theory



Toluene (92) | Acetic anhydride (102.09) | *p*-Methylacetophenone (134) | Acetic acid

The interaction between toluene and acetic anhydride in the presence of aluminium chloride gives rise to the formation of *p*-methylacetophenone and a mole of acetic acid is liberated.

4.7.3.2.3 Chemicals Required. Anhydrous powdered Aluminium chloride : 25 g ; Dry Toluene : 40 g ; Redistilled Acetic Anhydride : 8.66 g ; Conc. Hydrochloric acid : 50 ml ; Ether : 30 ml ; and NaOH Soln. [20% (w/v)] : 20 ml.

4.7.3.2.4 Procedure. The different steps involved in this synthesis are enumerated below sequentially :

(1) First of all equip a 250 ml three-necked flask with a double-surface condenser, a sealed stirrer assembly ; and a dropping funnel protected with a $CaCl_2$-guard tube. Connect the top of the condenser to a trap meant for absorbing the liberated HCl-gas.

(2) Transfer 25 g (0.56 mol) of pure anhydrous, finely powdered aluminium chloride, 40 g (46.66 ml ; 1.30 mol) of pure dry (absolute) toluene in the reaction flask ; and cool the contents of the flask in an ice-water bath (0–5°C).

(3) Introduce 8.66 g (8 ml ; 0.25 ml) of redistilled acetic anhydride through the dropping funnel into the reaction mixture very slowly in small lots at intervals over a span of 30 minutes with constant stirring with mechanical stirrer provided.

Note. The reaction is appreciably exothermic in nature.

(4) After addition of entire acetic anhydride, heat the contents of the flask on a boiling electric water-bath for nearly 30 minutes (or unless and until the evolution of HCl-gas ceases to evolve) to complete the ensuing reaction.

(5) Pour the cooled contents into a 250 ml beaker containing a mixture of 50 g of crushed ice and 50 ml of conc. HCl. Stir the contents with a glass rod until all the aluminium salts get dissolved more or less completely.

(6) Transfer the resultant mixture to a separating funnel, add 15 ml of ether, shake and separate the **upper** (largely toluene) layer.

(7) Extract the **lower** aqueous layer with another 15 ml of ether and add this to the previously collected toluene solution.

(8) Wash the combined toluene and ether extracts with 20 ml of NaOH aqueous (20% w/v) solution (or until the washings give a distinct test for alkalinity), subsequently with water, separate the organic layer and dry it with either $MgSO_4$ or fused anhydrous $CaCl_2$.

(9) Remove the ether (~ bp 36°C) and benzene (~ 80°C) by distillation under vacuo through a short fractionating column.

(10) *p*-Methylacetophenone is collected at 93–94°C/7 mm Hg with a yield of 9.5 g.

4.7.3.2.5 Precautions

(1) The three ingredients *viz.,* toluene, aluminium chloride, and acetic anhydride must be absolutely dry or anhydrous in quality so as to accomplish optimized reaction and, hence, maximum yield (the reported, yield ranges between 84 to 86%).

(2) The addition of acetic anhydride to the reaction mixture containing toluene and $AlCl_3$ should be done very cautiously at a low pace with constant stirring and chilling because this stage is very critical due to the exothermic nature of the reaction.

(3) Washing the combined toluene and ethereal extract with aqueous NaOH solution helps in removing the generated acetic acid as water-soluble sodium acetate.

(4) Distillation is advisably performed under reduced pressure so as to get the three fractions of *ether, toluene* and *p-methylacetophenone* separately and in a rather purer form.

4.7.3.2.6 Theoretical Yield/Practical Yield

The theoretical yield is calculated from the equation under theory (section 4.7.3.2.2) as mentioned below :

92 g of Toluene on interaction with 102.09 g of Acetic Anhydride

produces *p*-Methylacetophenone = 134 g

$\therefore$ 40 g of Toluene shall yield *p*-Methylacetophenone $= \frac{134}{92} \times 40 = 58.26$ g

Hence, Theoretical yield of *p*-Methylacetophenone = **58.26 g**

Reported Practical Yield = 9.5 g

Therefore, Percentage Practical Yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{9.5}{58.26} \times 100 =$ **16.30**

4.7.3.2.7 Uses

(1) *p*-Methylacetophenone has been found to be very useful with patchouli alcohol (*i.e.,* a tricyclic sesquiterpene alcohol isolated from oil of patchouli obtained from *Valeriana officinalis* L. (fam : *Valerianaceae*) : valerian.

(2) It is usually employed as a replacement for coumarin which is a pharmaceutic aid (flavour).

4.7.3.2.8 Questions for *Viva-Voce*

(1) Why is it essentially required to employ perfectly anhydrous reactants in the present synthesis ?

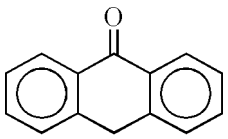
(2) Which stage of the on-going synthesis is usually exothermic in nature ? Explain !

(3) How would you get rid of the generated acetic acid from the reaction mixture ?

(4) Name the three products obtained by the distillation of the final reaction mixture under *vacuo* ?

4.7.3.3 Anthrone

4.7.3.3.1 Chemical Structure



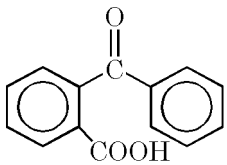
Anthrone

4.7.3.3.2 Synonyms. 9(10H)–Anthracenone ; 9, 10-Dihydro-9-oxanthracene ; Carbothrone.

Anthrone may be prepared from phthalic anhydride in a *three-step synthesis* as described below explicitely :

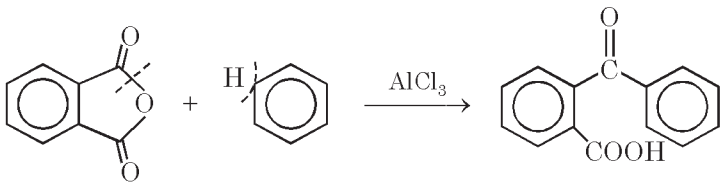
Step-I. Preparation of *o*-Benzoylbenzoic Acid

1. Chemical Structure



o-Benzoylbenzoic acid

2. Theory



Phthalic anhydride Benzene *o*-Benzoylbenzoic acid

Phthalic anhydride and benzene reacts in the presence of finely powdered anhydrous aluminium chloride, acting as a catalyst, to cleave the anhydride and produces *o*-benzoyl-benzoic acid. The above reaction usually takes place in an absolute anhydrous conditions only.

3. Chemicals Required. Phthalic anhydride : 10 g ; Benzene : 40 ml ; Anhydrous finely powdered $AlCl_3$: 20 g ; Anhydrous sodium bicarbonate : 6 g ; and concentrated Hydrochloric Acid : 25 ml.

4. Procedure. The various steps are as follows :

(1) Place 10 g of finely powdered phthalic anhydride and 40 ml dry and pure benzene in a 250 ml round bottom flask fitted with a reflux condenser.

(2) Add to the flask 20 g of finely powdered aluminium chloride in portions of 4 g at a time with constant shaking of the flask. Initiate the reaction by heating gently the contents of the flask on a water-bath for a few seconds only. In case, the reaction turns out to be vigorous and violent it is required to cool the contents of the flask in an ice-bath.

(3) Once the addition of $AlCl_3$ is complete, install the reflux condenser and reflux the contents on a pre-heated electric water bath for a duration of 2.5 to 3 hours *i.e.,* when the evolution of gases almost ceases completely.

(4) Cool the contents of the flask and add to it about 25 g of crushed ice to decompose the dark-coloured product. Add to it nearly 15 ml concentrated hydrochloric acid slowly till the resulting solution becomes virtually clear.

(5) Subject the reaction mixture to steam-distillation when benzene gets distilled.

(6) Allow the resultant liquid to cool down in an ice-bath when the crude *o*-benzoylbenzoic acid gets separated.

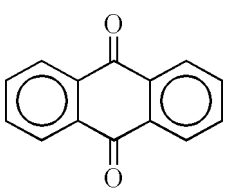
(7) Decant off the aqueous layer, and add to it a hot solution of 6 g anhydrous sodium carbonate in 80 ml water and heat gently over an water-bath. Filter the solution while hot, cool the filtrate to ambient temperature.

(8) Neutralize the resulting solution with 10 ml concentrated hydrochloric acid with occasional stirring and coolling the contents in an ice-bath when *o*-benzoylbenzoic acid separates out. Filter the solid product on a Büchner funnel under suction, wash with a little cold water and dry it by pressing between the folds of filter paper.

The yield of *o*-benzoyl benzoic acid is 12.6 g having mp 94°C.

Step-II. Preparation of Anthraquinone

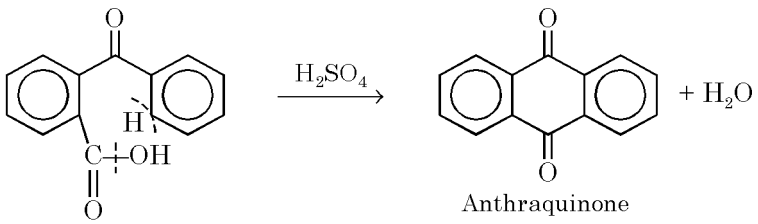
1. Chemical Structure



Anthraquinone

2. Synonyms. 9, 10-Anthracenedione ; 9,10-Anthraquinone ; 9,10-Dioxoanthracene ; Morkit.

3. Theory



o-Benzoylbenzoic acid Anthraquinone

In the presence of a strong dehydrating agent *e.g.,* fuming sulphuric acid (20% oleum) the molecule of *o*-benzoylbenzoic acid loses a molecule of water ; and thereby the closure of the middle ring (cyclization) is afforded with the formation of the desired compound anthraquinone.

4. Chemicals Required. *o*-Benzoylbenzoic acid : 10 g ; Fuming sulphuric acid : 45 ml.

5. Procedure. Various steps taking place are as follows :

(1) Mix intimately 10 g of *o*-benzoylbenzoic acid (Step-I) along with 45 ml of fuming sulphuric acid in a 250 ml conical flask. Heat the contents of the flask over a water bath for 2 hours preferably in a fume-cup-board.

(2) Allow the reaction mixture to cool and attain the room temperature ; and pour the contents directly into a 600 ml beaker containing 300 g of crushed ice with vigorous stirring with a glass rod when light-yellow crystals of anthraquinone separates out.

(3) Filter the product in a Büchner funnel with suction, wash with a little warm water, followed by dilute NH_4OH solution and finally with water.

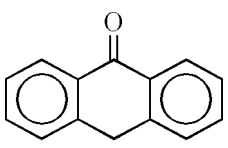
The yield of crude anthraquinone mp 283°C is 6.9 g.

6. Recrystallization. The crude product is recrystallized from a minimum quantity of hot acetic acid. The yield of the product is 6.75 g having mp 285-286°C.

7. Physical Parameters. Anthraquinone is obtained as light-yellow, slender monoclinic prisms by sublimation *in vacuo.* It is almost colourless, orthorhombic, bipyramidal crystals obtained from $H_2SO_4 + H_2O$. Its physical characteristics are : d_4^{20} 1.42–1.44 ; mp 286°C ; bp_{760}. 377°C. It is found to be insoluble in water. Its solubility profile (g/100 g) in ethanol at 18°C : 0.05 ; in boiling ethanol : 2.25 ; in ether at 25°C : 0.11 ; in chloroform at 20°C : 0.61 ; in benzene at 20°C : 0.26 ; and in toluene at 25°C : 0.30.

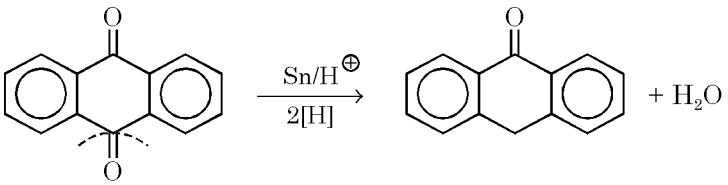
Step-III. Preparation of Anthrone

1. Chemical Structure



Anthrone

2. Theory



Anthraquinone (208.22) Anthrone (194.23)

The anthraquinone when subjected to reduction in the presence of tin metal and a mineral acid, such as : hydrochloric acid, one of the ketonic oxygen atoms gets knocked out as a molecule of water leaving behind a tricyclic structure having only one ketonic function. The resultant modified version of anthraquinone is known as anthrone.

3. Chemicals Required. Anthraquinone : 5 g ; Granulated Tin (metal) : 5 g ; Glacial acetic acid : 37 ml ; and concentrated Hydrochloric Acid (12 N) : 13 ml.

4. Procedure. The steps undertaken are as follows :

(1) Transfer 5 g of anthraquinone in a 250 ml round bottom quick-fit assembly, and add to it 5 g granulated tin (metal) plus 37 ml glacial acetic acid.

(2) Attach a reflux condenser and reflux the mixture* for 30–40 minutes on a heating mantle **without circulating water through the condenser.**

(3) Allow to cool the contents of the flask and then introduce dropwise 13 ml concentrated HCl through a dropping funnel.

Note. In case, the anthraquinone fails to undergo complete dissolution, add some more granulated tin and HCl.

(4) Filter and dilute the filtrate with 10 ml of water. Cool the resulting solution in an ice-bath when crystals of *anthraquinone* start separating out.

(5) Filter the crude anthraquinone in a Büchner funnel under suction, wash the residue with water, and finally dry by pressing between the folds of filter paper.

The yield of anthrone is 2.9 g and mp 153–154°C.

5. Precautions

(1) It must be ensured that the anthraquinone is completely reduced to anthrone. If need be a slight excess of Sn metal and conc. HCl may be added.

(2) Addition of concentrated HCl to the admixture of anthraquinone and acetic acid should be very gradual and with frequent shaking the contents.

6. Recrystallization. The crude anthrone may be recrystallized quite conveniently by dissolving it in a minimum quantity of a mixture of benzene and petroleum ether (3 : 1). The yield of the pure product mp 154.5–155°C is 2.75 g.

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* As the bp of glacial acetic acid is 118°C, hence **no water** is required to be circulated through the reflux condenser, otherwise it will crack immediately.

7. Theoretical Yield/Practical Yield. The theoretical yield calculated from the equation under theory (section. 2) is as stated under :

208.22 g of Anthraquinone on reduction yields Anthrone = 194.23 g

$\therefore$ 5 g of Anthraquinone shall yield Anthrone $= \dfrac{194.23}{208.22} \times 5 = 4.66$ g

Hence, Theoretical Yield of Anthrone = **4.66 g**

Reported Practical Yield = 2.90 g.

Therefore, Percentage Practical Yield $= \dfrac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

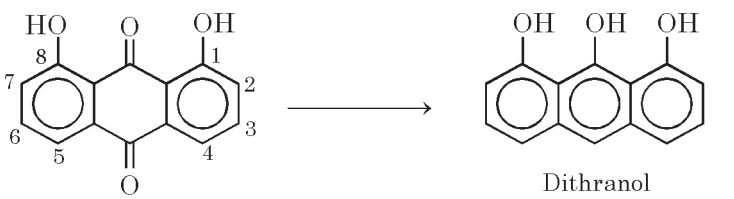
$= \dfrac{2.90}{4.66} \times 100 =$ **62.23**

8. Physical Parameters. Anthrone is obtained as orthorhombic needles from benzene and petroleum ether having mp 150°C. It is found to be soluble in most organic solvents without producing any fluorescence. However, any fluorescence present is solely due to anthranol. It has an inherent tendency to get converted to anthraquinone perhaps due to atmospheric oxidation. Its observed equilibrium in absolute alcohol are : 89% anthrone ; and 11% anthranol.

9. Uses

(1) Anthrone or its tautomer *anthrol* or its hydroxy derivatives (*i.e.,* the aglycones) are found to exert purgative effects. However, the anthraquinone glycosides are usually present in several herbal drugs, such as : *senna, cascara, rhubarb* and *aloes.*

(2) Dithranol, used in ointments in a host of skin affections, is the *anthrol* duly formed by reduction of 1, 8-dihydroxyanthraquinone as shown below :



1, 8-Dihydroxy-anthraquinone

Dithranol
(1, 8, 9-Anthracenetriol)

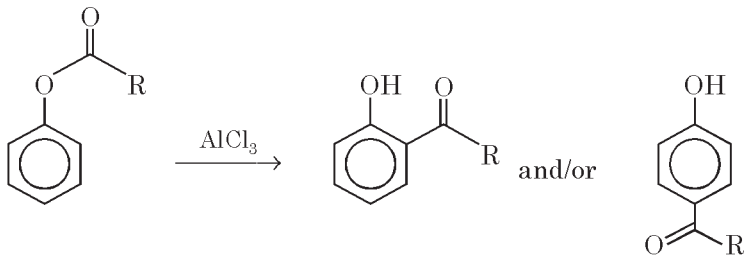
10. Questions for *Viva-Voce*

(1) How would you obtain anthrone with the help of Friedel-Crafts Reaction ?

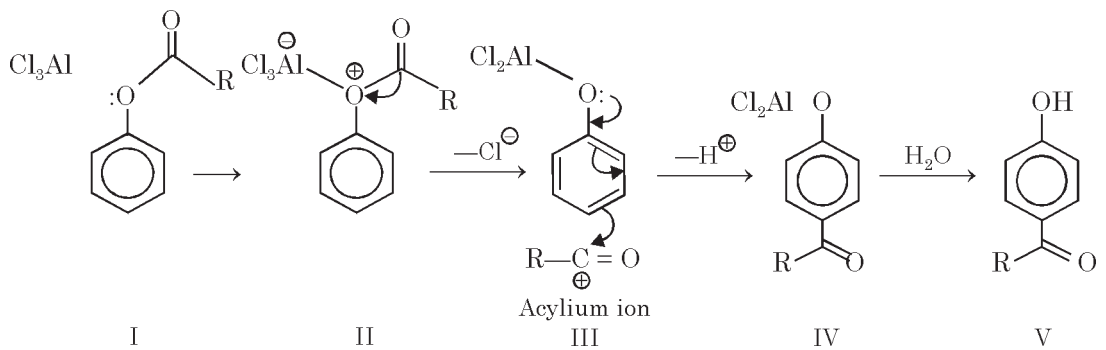
(2) 'Phthalic anhydride undergoes Friedel-Crafts reaction with benzene to yield *ortho*-benzoyl benzoic acid, which gets cyclized to anthraquinone, and it gets reduced to produce anthrone'. Explain the sequence of reactions involved briefly.

4.7.4 Fries Reaction

The rearrangement of phenolic esters to either *o*-and/or *p*-phenolic ketones on being heated upon with anhydrous aluminium chloride or other Lewis acid catalysts is known as **Fries Reaction*** or **Rearrangement**, as depicted below :



Mechanism of Reaction. It is, however, pertinent to mention here that the exact details of the mechanism of the Fries Reaction or Rearrangement are quite uncertain but the reaction probably encounters the possible formation and migration of the acylium ion as shown under :



Phenolic ester (I) bears a lone pair of electrons on the phenolic O-atom and a mole of aluminium chloride. A drift of electron from the carbonyl function $\left(\begin{matrix}O\\ \|\\ -C\end{matrix}\right)$ to the phenolic O-atom helps in establishing a covalent bond between $AlCl_3$ and phenolic O-atom (II) whereby the $AlCl_3$ possesses a –ve charge and the phenolic O-atom a +ve charge. Thus, the intermediate (II) is a salt. Further, II loses a chloride ion thereby forming a covalent bond between $AlCl_2$ moiety and phenolic O-atom. The presence of an acyllium ion triggers the shift of electrons right from the top of the phenolic O-atom down to the C-atom in the acyllium ion in an orderly sequence to yield (III). The product (III) loses a proton thereby forming an ester linkage at the *para*-position and a Cl_2Al bond with the phenolic O-atom, thus generating (IV). Finally, the product (IV) undergoes hydrolysis to produce a *para*-hydroxy phenolic ketone (V).

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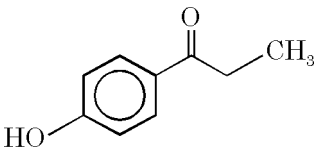
*Fries, K., and G. Fink. *Ber.* **41**, 4271 (1908) ;

Anderson, J.C., and C.B. Reese, *Photo-Fries Rearrangement*, *Proc. Chem. Soc. 217 (1960).*

4.7.4.1 *p*-Hydroxypropiophenone

4.7.4.1.1 Chemical Structure

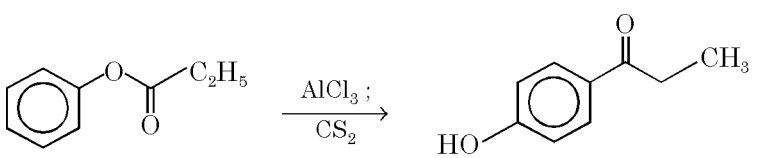


p-Hydroxypropiophenone

4.7.4.1.2 Synonyms

4′-Hydroxypropiophenone ; Paroxypropione ; 1 – (4-Hydroxyphenyl)-1-propanone ; *para*-Oxypropiophenone ; *p*-Propionylphenol ; Ethyl-*p*-hydroxyphenyl ketone ; B-360 ; H-365 ; Prophenone ; Frenatol ; Frenohypon ; Paroxon ; Possipione ; Hypostat ;

4.7.4.1.3 Theory



Phenyl propanoate (150)

p-Hydroxypropiophenone (150.18)

The interaction between phenylpropanoate and anhydrous aluminium chloride in a medium of carbon dislphide gives rise to the formation of *p*-hydroxypropiophenone. However, experimenlally the *para*-isomer is obtained in a relatively higher yield (50%) with respect to the corresponding *ortho*-isomer (35%).

Interestingly, the IR and PMR-spectra of both the above isomers put forward valuable informations distinguishing them as may be observed from the following available data :

S. No.	Spectral Features	*p*-Hydroxypropiophenone	*o*-Hydroxypropiophenone	Remarks
1.	IR-Spectrum	Absorptions between 700-800 cm^{-1}	Absorptions between 700-800 cm^{-1}	Confirms the respective *o*- and *p*-substitutions.
2.	PMR-Spectrum	(DMSO-d_6) shows evident signals at δ1.10 (*t*, 3H, Me) 2.92 (*q*, 2H, CH_2), 6.90 (*d*, 2H, *ortho*-H's to COE*t* and 7.88 (*d*, 2H, *ortho*-H's to OH) ;	($CDCl_3$, TMS)-Displays distinct signals at δ1.19, (*t*, 3H, Me), 2.93 (*q*, 2H, CH_2), 6.60 – 7.75 (*m*, 5H, CAR–H), and 12, 13 (S, 1H, OH) ;	In *para*-isomer the hydroxy (OH) **proton** is not observed.

4.7.4.1.4 Chemicals Required. Anhydrous pure Aluminium Chloride : 37.4 g ; Carbon disulphide : 40 ml ; Phenyl propanoate : 37.6 g ; Dilute Hydrochloric acid (6N) : 30 ml ; and Methanol : 50 ml.

4.7.4.1.5 Procedure. Various steps involved are as given below :

(1) Set up a 250 ml three-necked flask fitted with a dropping funnel, an efficient double-surface reflux condenser and a heavy-duty variable speed mechanical stirrer.

(2) Transfer 37.4 g (1.4 mol) finely powdered aluminium chloride and 40 ml carbon disulphide into the flask ; attach a gas-absorption trap to the top-end of the reflux condenser.

(3) Stir the suspension and introduce 37.6 g (35.8 ml ; 1.25 mol) of phenyl propanoate very slowly and carefully and at such a rate so that the solvent boils steadily and vigorously for a duration of 90-100 minutes. During this period enough HCl-gas is evolved and is subsequently absorbed by the trap provided.

(4) After the complete addition of phenyl propanoate, gently reflux the reaction mixture over an electric water bath until the HCl-gas has ceased to evolve anymore (approximately 2 hours).

(5) Attach a goose-neck adapter to reposition the condenser downwards, and distill off the solvent from the water bath.

[**Note :** *CS_2 – is **poisonous** and highly refractive, mobile, very inflammable liquid (bp + 46.5 °C).*]

(6) Transfer the reaction flask to a pre-heated oil-bath maintained at 145 ± 5 °C and continue heating with stirring, for a period of 3 hours. During this process more HCl-gas is evolved, the mixture gets thickened, and finally turns into a *brown resinous mass* ; continue the stirring as long as it is convenient and feasible.

(7) The reaction mixture is allowed to cool, and the aluminium chloride complex is decomposed by **slowly** adding first 50 ml of dilute HCl, followed by 80 ml of water ; thus, sufficient heat is evolved and a dark oil gets collected on the surface. Allow it to stand overnight, when major quantum of the *para*-hydroxy propiophenone in the upper layer solidifies.

(8) Filter off the solid product in the Büchner funnel under suction, wash it with cold water and dry it in the folds of filter paper.

The crude product has a yield of 15.25 g having *mp* ranging between 144-146°C.

4.7.4.1.6 Precautions

(1) The addition of phenyl propanoate into the mixture of aluminium chloride and carbon disulphide must be done very slowly and over a stretch of 90-100 minutes.

(2) The gas absorption trap provided at the top of the reflux condenser must be efficient to absorb the HCl-gas evolved.

(3) Completion of the reaction, after removal of the solvent CS_2 (bp 46.5°C), in an oil bath at 145 ± 5°C for 3 hours is an absolute necessity so as to obtain a brown resinous product.

(4) The unreacted residual $AlCl_3$ and the $AlCl_3$-complex is usually decomped by the addition of dilute HCl followed by water ; and to finally obtain a dark oil floating on the surface of water.

4.7.4.1.7 Recrystallisation

Dissolve the crude *p*-hydroxypropio-phenone in 50 ml of methanol, and warm it over an electric water-bath to effect faster dissolution and allow it to cool overnight in a refrigerator. Filter off the pale yellow recrystallized solid in a Büchner funnel under suction and dry it in the air or in a vacuum desiccator. The yield of the pure product is 14.6 g having mp 146.5-147°C.

4.7.4.1.8 Theoretical Yield/Practical Yield

The theoretical yield is calculated from the equation under theory (section 4.7.4.1.3) as given below :

150 g of Phenyl propanoate on reaction with 37.4 g of $AlCl_3$ yields

p-Hydroxypropiophenone = 150.18 g

$\therefore$ 37.6 g of Phenyl propanoate shall yield *p*-Hydroxypropiophenone

$$= \frac{150.18}{150} \times 37.6 = 37.65 \text{ g}$$

Hence, Theoretical yield of *p*-Hydroxypropiophenone = **37.65 g**

Reported Practical yield = 15.25 g

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$$= \frac{15.25}{37.65} \times 100 = \mathbf{40.50}$$

4.7.4.1.9 Physical Parameters. Paroxypropione is obtained as needles or prisms from water having mp 149°C. Its solubility in water is : 1 part in 2896 parts of water at 15°C ; and in 30 parts at 100°C. However, it is freely soluble in ether and ethanol.

4.7.4.1.10 Uses

(1) It is employed as an effective pituitary gonadotropic hormone inhibitor.

(2) It has been used for the control and management of pituitary hyperactivity.

4.7.4.1.11 Questions for *Viva-Voce*

(1) How would you differentiate between the *para-* and *ortho*-hydroxypropiophenone by the help of PMR-spectrum ?

(2) Why is HCl-gas evolved from the reaction mixture ? Explain.

(3) Why is it necessary to get rid of the solvent (CS_2) first before subjecting it to heating in an oil bath for 3 hours to complete the reaction ?

(4) How would you decompose the $AlCl_3$-complex in the final reaction mixture ? Explain.

4.7.5 Grignard Reaction

In a broader perspective the **Grignard Reaction*** is the addition of organomagnesium compounds, precisely termed as Grignard reagents, to specifically the carbonyl compounds $\left(\begin{array}{c} O \\ \| \\ -C- \end{array}\right)$ to yield **alcohols.** It is, however, pertinent to mention here that a more modern interpretation also exists which further extends the horizon and scope of the reaction to include

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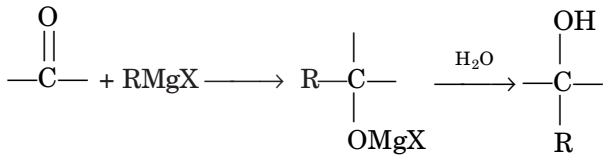
* Grignard. V., *Compt. Rend,* **130,** 1322 (1900) ;

Huryn, D.M., *Review of stereo selective addition of carbonyl compounds, Comp. Org. Syn.*, **1,** 49-75 (1991).

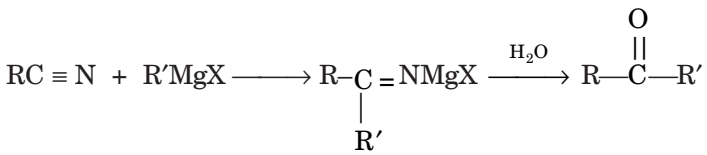
the addition of Grignard reagents to a wide variety of **electrophilic substrates**, as exemplified below :

(*a*)



Carbonyl compound | Grignard Reagent | An Intermediate | An Alcohol

(*b*)



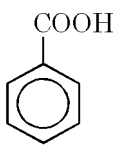
A Nitrile or Cyano compound | Grignard Reagent | An Intermediate | A Ketone

In Equation (*a*) the carbonyl compound is made to react with a Grignard reagent to form an intermediate, which upon subsequent hydrolysis gives rise to **an alcohol.**

The Equation (*b*) depicts the interaction between a nitrile or a cyano compound and a Grignard reagent to yield an intermediate bearing the two alkyl groups, which undergoes hydrolysis to produce **a ketone.**

4.7.5.1 Benzoic Acid

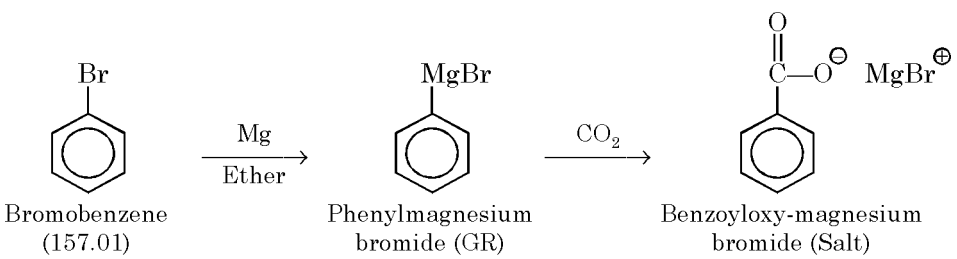
4.7.5.1.1 Chemical Structure



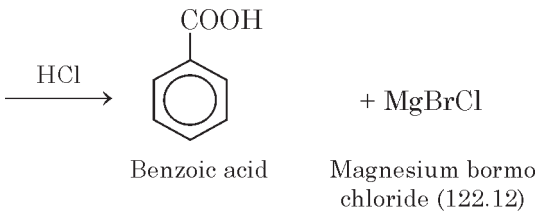
Benzoic acid

4.7.5.1.2 Synonyms. Benzenecarboxylic acid ; Phenylformic acid ; Dracylic acid ;

4.7.5.1.3 Theory



Bromobenzene (157.01) | Phenylmagnesium bromide (GR) | Benzoyloxy-magnesium bromide (Salt)



First, bromobenzene reacts with magnesium (metal) to yield the Grignard Reagent (GR)-phenyl magnesium bromide, which reacts with carbon dioxide to yield the corresponding salt *viz*., benzoyloxy-magnesium bromide. The resulting salt on subsequent hydrolysis with HCl ultimately produces benzoic acid and magnesium bromochloride gets eliminated.

4.7.5.1.4 Chemicals Required. Dry Magnesium turnings : 2.4 g ; Sodium Dry Ether : 30 ml ; Dry Bromobenzene : 15.7 g (10 ml) ; Iodine Crystals : 0.1 g ; and Dilute Hydrochloric Acid (6 N) : q.s. ;

4.7.5.1.5 Procedure. The various steps involved are stated as under :

(1) Transfer 2.4 g of dry magnesium turnings and 30 ml of sodium dry ether in a 250 ml round bottom flask fitted with an efficient reflux condenser.

(2) Add to the reaction flask slowly and carefully 15.7 g (10 ml) of absolutely dry bromobenzene along with a crystal of iodine. An immediate commencement of reaction shall take place thereby turning the etherial layer to milky white. In case, the reaction does not start off, warm the contents of the flask gently on an electric water-bath and remove it from the water-bath after the mixture starts refluxing.

(3) Once the reaction starts, the heat generated from it will promote the reaction itself. Boil the contents of the flask gently for a duration of 50-60 minutes.

(4) Place separately 20 g of crushed ice in a 250 ml beaker and pour into it slowly the Grignard reagent prepared earlier with constant vigorous stirring. A quick forceful reaction ensues and the contents in the flask happen to turn into a pasty mass. Continue stirring the mass till all CO_2 cease to evolve.

(5) Add 50 ml of warm water and subsequently acidify the contents with dilute HCl carefully to litmus paper ; thus benzoic acid shall start separating out and the magnesium salt will get dissolved. Cool the contents of the beaker in an ice-bath and filter the white residue in a Büchner funnel under suction, wash with water and air dry the product.

The yield of the crude product is 6.4 g having mp 119-120.5°C.

4.7.5.1.6 Precautions

(1) The bromobenzene must be added very slowly and carefully into the mixture of Mg turnings plus dry ether.

(2) Pour the Grignard reagent gradually into a mixture of crushed ice, when CO_2 starts evolving with the formation of the corresponding salt.

(3) Acidification with dilute hydrochloric acid is done cautiously to obtain the desired product benzoic acid.

4.7.5.1.7 Recrystallization. Dissolve the crude product with minimum amount of hot water and allow it to cool overnight in a refrigerator when leaflets of benzoic acid is obtained. Collect the residue in a Büchner funnel and dry it in an oven at 90°C for 1 hour. The yield of the pure product is 6.1 g mp 121-122°C.

4.7.5.1.8 Theoretical Yield/Practical Yield. The theoretical yield is calculated from the equation under theory (section 4.7.5.1.3) as given below :

157.01 g of Bromobenzene after Grignardization

yield Benzoic Acid = 122.12 g

$\therefore$ 15.7 g of Bromobenzene shall yield Benzoic Acid $= \frac{122.12}{157.01} \times 15.7 = 12.20$ g

Hence, Theoretical yield of Benzoic Acid = **12.20 g**

Reported Practical yield = 6.4 g

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{6.40}{12.20} \times 100 = \mathbf{52.45}$

4.7.5.1.9 Physical Parameters. It is obtained as monoclinic tablets, plates, leaflets having d : 1.321, mp 122.4°C, bp_{760} 249.2°C, begins to sublime at ~ 100°C. It is found to be volatile with steam. Its flash point ranges between 121-131°C. Its dissociation constant at 25°C : 6.40×10^{-5} ; and the pH of saturated solution at 25°C : 2.8. Its solubility in water ($g.L^{-1}$) at 25°C = 3.4 ; at 50°C = 9.5 ; at 80°C = 27.5 ; and at 95°C = 68.0. The solubility in water is enhanced by alkaline substances, for instance : borax, trisodium phosphate.

Solubility Profile. 1 g dissolves in 2.3 ml cold alcohol ; 1.5 ml boiling alcohol ; 4.5 ml chloroform ; 3 ml ether ; 3ml acetone ; 30 ml carbon disulphide ; 30 ml carbon tetrachloride ; 10 ml benzene ; 23 ml oil of turpentine ; also soluble in volatile and fixed oils ; and slightly in petroleum ether.

4.7.5.1.10 Uses

(1) It is invariably employed as a keratolytic* in ointments.

(2) It is abundantly used in food preservation.

(3) It has been employed with salicylic acid as a topical antifungal agent.

(4) It is used for curing tobacco.

(5) It finds its usage as a mordant in calico printing.

(6) It is used in the manufacture of benzoates *e.g.*, sodium benzoate.

4.7.5.1.11 Questions for *Viva/Voce*

(1) What is the significance of Grignard reaction in medicinal chemistry ?

(2) How would you explain the reaction of Grignard reagent (R-Mg-X) on a carbonyl compound and a nitrile (cyano) compound ?

(3) Why is it necessary to use absolutely dry Mg-turnings, ether and bromobenzene and a few crystals of iodine to initiate the formation of Grignard Reagent ?

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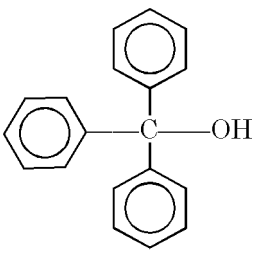
*__Keratolytic.__ An agent that causes or promotes shedding of the skin at regular intervals.

4.7.5.2 Triphenylcarbinol

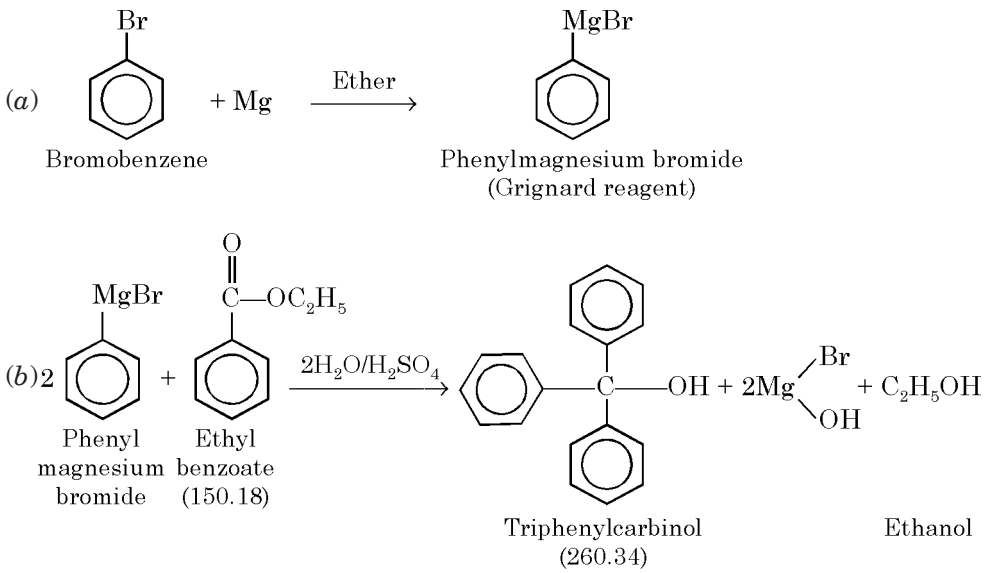
4.7.5.2.1 Chemical Structure



Triphenylcarbinol

4.7.5.2.2. Synonyms. Triphenylmethanol ; Tritanol ;

4.7.5.2.3 Theory



In Equation (*a*) bromobenzene reacts with magnesium in the presence of ether to yield phenyl magnesium bromide *i.e.*, the Grignard Reagent.

In Equation (*b*) the Grignard reagent obtained from Eq. (*a*) interacts with ethyl benzoate in the presence of water and sulphuric acid to give rise to the formation of triphenyl carbinol, ethanol, and magnesium bromohydroxide.

The synthesis of triphenylcarbinol is divided into **two** parts, namely :

(*a*) Preparation of Phenyl magnesium bromide (Grignard Reagent).

(*b*) Preparation of Triphenylcarbinol.

Part-I : Phenyl Magnesium Bromide

1. **Chemicals Required.** Bromobenzene : 10.5 ml ; Magnesium ribbon or powder : 2.5 g ; Dry Ether : 75 ml ; Ethyl benzoate : 5 ml ; Dilute sulphuric acid (6N) : 120 ml ; and Sodium hydrogen sulphite ($NaHSO_3$) : 0.5 g.

2. Procedure. The steps followed in this synthesis are enumerated as under :

(1) Set up a 250 ml round bottom flask filled with a reflux condenser the top-end of which is provided with a $CaCl_2$-guard tube.

[**Note :** *It is absolutely important that all glass apparatus must be perfectly dry.*]

(2) Transfer 2.5 g magnesium ribbon or powder into the reaction flask and add to it 15 ml of dry ether plus a few crystals of iodine.

(3) Dissolve separately 10.5 ml of dry bromobenzene in 50 ml of dry ether ; and add about 30 ml of this solution to the magnesium suspended in the ether by removing the condenser for a moment. In case, no reaction commences of its own within a span of 5-10 minutes, warm the flask gently on a pre-heated electric water-bath until the reaction starts, that may be evidently observed by the *appearance of cloudiness* and *disappearance of* I_2 *crystals.*

(4) The reaction continues with brisk vigour until the ether starts boiling. Take note of the situation when the boiling process of ether has almost ceased, add 10 ml portion of the remaining solution of bromobenzene in ether [prepared in (3) above] by again removing the $CaCl_2$-guard tube for a few seconds. Allow the reaction to proceed vigorously and when it seems to have slowed down add the remaining ethereal solution of bromobenzene as done before.

(5) When the addition of bromobenzene in ether is complete, and the vigorous reaction is almost ceased, transfer the reaction flask to a water-bath and heat under reflux for a further duration of 30 to 45 minutes. The clear solution thus obtained is that of phenyl magnesium bromide (Grignard Reagent).

Part-II : Triphenylcarbinol

1. Procedure. The various steps incurred are as follows :

(1) Take the flask containing Grignard Reagent (in PART-I) away from the electric water bath, cool and add to it a solution of 5 ml dry ethyl benzoate dissolved in 15 ml of dry ether very slowly down the reflux condenser ; adding only in small lots at inervals. The contents of the reaction flask is shaken in between the additions in order to ascertain thorough mixing of reactants.

[**Note :** *In case, excessive and vigorous boiling of ether takes place, cool the contents of the flask by immersing in a cold water bath to control the on going reaction.*]

(2) Once the reaction almost subsides the reaction flask is heated under reflux on an electric water bath for a duration of 30-35 minutes.

(3) Cool the reaction flask to room temperature and pour the contents of the flask into a 500 ml beaker containing 100 g of crushed ice and 60 ml of dilute sulphuric acid (6N). The content is stirred vigorously with a glass rod so as to decompose the magnesium derivative, and the resulting triphenylcarbinol gets dissolved in ether. In case, any residue is left behind, add a little more ether to dissolve the same. Transfer the total contents into a separating funnel and **discard the lower aqueous layer.**

(4) The upper ethereal layer is first shaken with two portions each of 30 ml dilute sulphuric acid (6N) ; and rejecting the lower aqueous layer. The ethereal layer is washed

with 25 ml water containing 0.5 g sodium bisulphite to get rid of the iodine completely.

(5) The treated ethereal layer is transferred to a 500 ml round bottom flask ; and the ether is distilled off on an electric water bath carefully.

[**Caution : Ether is highly inflammable**].

(6) Add to the residual portion in the flask 50 ml of water and fit the flask for steam distillation. Now, steam distil the contents for 30 minute, or till such time when no further oil passes over (*i.e,* unreacted ethyl banzoate and Grignard reagent). **Discard the distillate.**

(7) The residue in the round bottom flask gets solidified on cooling. Filter the product in a Büchner funnel under suction, wash with a little cold water, drain well with an inverted glass stopper, and ultimately dry the product by pressing between the folds of filter paper sheets.

The yield of the crude product is 8.4 g mp 159-161°C.

2. Precautions

(1) Add the ethereal solution of ethyl benzoate into the Grignard reagent in small lots at intervals only with frequent shaking.

(2) The magnesium derivative (*i.e.,* MgBrOH) obtained as a byproduct has got to be decomposed completely by adding dilute H_2SO_4 and crushed ice.

(3) The ethereal layer is washed with water and sodium bisulphite solution to remove the traces of iodine, if any, in PART-I.

(4) Steam distillation is an important step to remove the unreacted ethyl benzoate and Grignard Reagent.

3. Recrystallization. Dissolve the crude product in rectified spirit or benzene or carbon tetrachloride when beautiful crystals of pure triphenylcarbinol is obtained. The yield of the pure product is 7.9 g having mp 163.5-164.2°C.

4. Theoretical Yield/Practical Yield. The theoretical yield is calculated from the equations (*a*) and (*b*) (in section 4.7.5.2.3) under theory as given below :

150.18 g of Ethylbenzoate on reaction with Phenyl magnesium bromide

(Grignard Reagent) yields Triphenylcarbinol = 260.34 g

$\therefore$ 5.25 g* of Ethyl benzoate shall yield Triphenylcarbinol $= \frac{260.34}{150.18} \times 5.25 = 9.1$ g

Hence, Theoretical yield of Triphenylcarbinol = **9.1 g**

Reported Practical yield = 8.4 g

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{8.4}{9.1} \times 100 =$ **92.30**

* The d_4^{25} for Ethylbenzoate is 1.050.

5. Physical Parameters. Triphenylcarbinol is obtained as trigonal crystals from benzene : d_4^0 1.199 ; mp 164.2°C. It is found to be insoluble in water and petroleum ether. It is easily soluble in ethanol, ether and benzene. It is soluble in concentrated sulphuric acid and gives an intense yellow colouration. It is also soluble in glacial acetic acid but without any specific colouration.

6. Uses. It was shown that a mixture of solutions of triphenylcarbinol and trimethylsilyl trifluoromethanesulphonate in an equimolar proportion may be used as a reagent for the effective tritylation of a secondary hydroxyl group. [PMID : 10923195].

7. Questions for *Viva-Voce*

(1) Why are absolutely dry conditions required for this reaction ?

(2) Why do we add a few crystals of iodine in the Grignard reaction ?

(3) How would you decompose the magnesium derivative (*i.e.*, MgBr OH) formed as a byproduct ?

(4) Why is it necessary to steam distillate the mixture after removal of ether ?

4.7.6 Hoesch Reaction (or Houben-Hoesch Reaction)

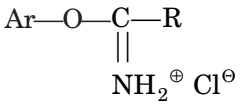
Friedel-Crafts acylation with nitriles and HCl is known as the *Hoesch* or the *Houben-Hoesch reaction.**

Generally, the Hoesch Reaction is exclusively employed for the introduction of the —COR group into the aromatic ring of a **phenol** or a **phenolic ether**, and invariably proceeds specifically with promptness and rapidity with **polyhydric phenols.** Some school of thoughts have gainfully used it in certain reactive *heterocyclic compounds*, such as : pyrrole ; however, it may also be extended to aromatic amines by the use of BCl_3.**

Silent Features. These are :

(1) In most cases, a *Lewis acid* is necessary ; and $ZnCl_2$ being the most common substance used,

(2) *Monohydric phenols* usually do not produce ketones,*** but instead are commonly attacked at the oxygen to produce imino esters,



An 1mino Ester

(3) A host of **nitriles** have been used.

(4) **Aryl nitriles** also give good results, if they are first treated with HCl and then $ZnCl_2$, and finally the substrate added at 0°C.****

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*For a review, see Ruske, in Olah : Friedel-Crafts and Related Reactions ; Wiley, New York, 1963-1964, Vol.1, pp. 91–115.

Sugasawa *et al*. *J. Org. Chem.,* **1979, *44*, 578.

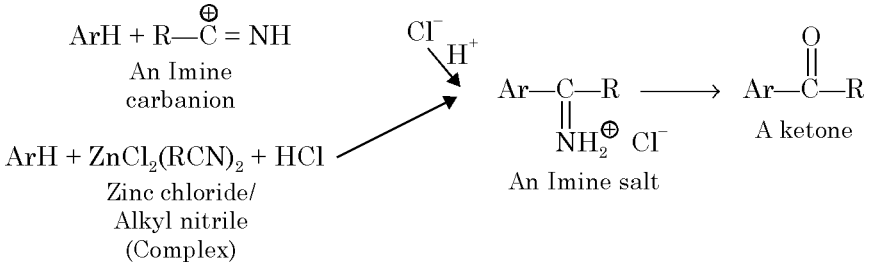
***Toyoda, Sesakura and Sugasawa, *J.Org. Chem.,* **1981**, *46*, 189.

****Zil'berman and Rybakova., *J. Gen. Chem.*, USSR, **1960**, *30*, 1972.

In actual practice, this procedure enhances yields with any nitrile.

5. In case, *thiocyanates* (RSCN) are employed, the corresponding thiol esters (Ar COSR) may be obtained.

Reaction Mechanism. Interestingly, the reaction mechanism seems to be quite complex, and, therefore, no logical and broadly acceptable mechanism has yet been put forward. However, a possible and probable reaction mechanism has been suggested which is as follows under :



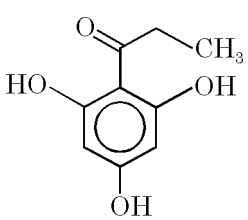
First stage of reaction essentially comprise of an attack on the substrate (*i.e.*, an aromatic hydrocarbon) by another species containing the *nitrile* and *HCl* (and also the Lewis acid, if present) to produce a corresponding **imine salt.** The possible and probable attacking species could be either *an imine carbanion* or *a zinc chloride/alkyl nitrile complex.*

Second stage, the resulting salts (*e.g.*, Imine salt) are duly hydrolyzed to give rise to the respective ketone.

Note. Ketones may also be prepared by the interaction of phenols or phenolic ethers with a nitrile in the presence of Fe_3CSO_2OH * ; however, the mechanism in this instance is entirely different.

4.7.6.1 Flopropione

4.7.6.1.1 Chemical Structure



Flopropione

4.7.6.1.2 Synonyms

Phloropropiophenone ; 1-(2,4,6-Trihydroxyphenyl)-1-propanone ; 2′, 4′, 6′-Trihydroxypropiophenone ;

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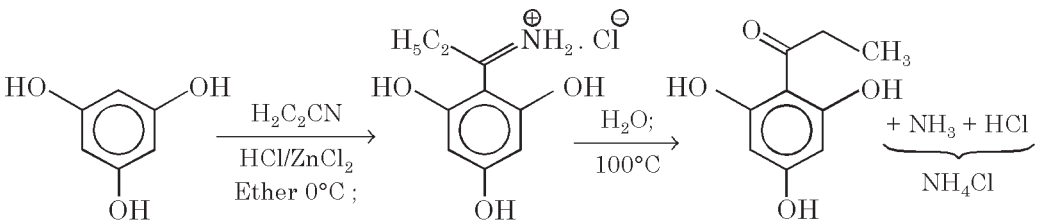
*Booth and Noori., *J. Chem. Soc., Perkin. Trans.* 1, **1980,** 2894 ; Amer, Both, Noori and Proenca, *J. Chem. Soc., Perkin Trans*. 1, **1983**, 1075.

4.7.6.1.3 Theory



Phloroglucinol (126.11) — An intermediate salt* — Flopropione (182.18)

Phloroglucinol when treated with propionitrile in the presence of zinc chloride and hydrochloric acid in a medium of ether maintained at 0°C gives rise to an intermediate salt. The resulting salt on being subjected to hydrolysis at 100°C yields the desired product flopropione** with the elimination of one mole each of ammonia and HCl that readily forms ammonium chloride.

4.7.6.1.4 Chemicals Required. Phloroglucinol : 25.2 g ; Anhydrous propionitrile : 22 g ; Sodium-dried Ether : 100 ml ; Fused zinc chloride : 5 g ; Decolourizing carbon : 6 g ;

4.7.6.1.5 Procedure

The various steps involved are as follows :

(1) Place 25.2 g (0.2 mol) of dry phloroglucinol, 22 g (28.14 ml, 0.4 mol) of anhydrous propionitrile, 100 ml of sodium-dried ether and 5 g of finely powdered fused zinc chloride in a 500 ml Büchner flask duly fitted with a wide gas inlet tube.

[**Note :** *The propionitrile may be dried either over anhydrous calcium sulphate or by distilling from* P_2O_5 (bp_{760} *97.2°C*).

(2) The side-arm of the Büchner flask is protected with a $CaCl_2$-guard-tube. Now, cool the flask in an ice-salt freezing mixture in an efficient fume cupboard, and pass a steady and brisk stream of dry HCl-gas*** through the solution for a duration of 2 hours with occasional shaking.

(3) The contents of the flask is allowed to chill overnight (24 hrs.) in an ice-chest (or refrigerator). Again pass dry HCl-gas into the pale yellow mixture for an additional period of 2 hours. Stopper the flask and leave it either in an ice-chest (or refrigerator) for 72 hours at a stretch.

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*Chlorozincate of Imine Salt.

Canter *et. al. J. Chem. Soc.*, 1245, (1931); Howells and Little., *J. Am. Chem. Soc.*, **54, 2451, (1932).

***__HCl-Gas :__ [From NH_4Cl + conc. H_2SO_4] : the conc. H_2SO_4 is made to react with lumps of fused ammonium chloride in a *Kipp's Apparatus* or a *Büchner Flask* fitted with a ground-glass joint to which is attached a dropping funnel. In the latter instant, NH_4Cl moistened with conc. HCl is kept in the flask and conc. H_2SO_4 is added dropwise from the funnel slowly so as to regulate evolution of HCL-gas. In either process the generated HCl-gas may be dried by passage through a **Drechsel Bottle** containing conc. H_2SO_4. The latter may be followed by an empty **Drechsel Bottle** as a precaution against "sucking-back" of the contents of the reaction flask.

(4) The appearance of a bulky yellowish-orange precipitate of the **intermediate salt** takes place. Decant the ethereal layer and wash the solid residue with two successive portions of sodium-dried ether, 25 ml each.

(5) Transfer the solid with the aid of about 1 L of hot water into a 2 L round bottomed flask filted with a quick-fit reflux condenser. Vigorously boil the yellowish solution for a span of 120 minutes, allow to cool somewhat, add 5-6 g of decolourizing carbon, boil the solution for additional 5-10 minutes ; and filter the hot solution with suction through a preheated Büchner funnel.

(6) Extract the decolourizing carbon on the filter paper with two 100 ml portions of boiling water, and add the filtrate to the main bulk of the aqueous portion. Allow the resulting solution to stand overnight, and filter the colourless needles of flopropione at the pump, dry at 120°C to get rid of the molecule of water of crystallization, and finally preserve the crude product in an air-tight glass bottle.

The yield of the crude product is 30.5 g having mp 173-174°C.

4.7.6.1.6. Precautions

(1) All glass apparatus used in carrying out the reaction must be in perfect absolute dry condition.

(2) All the reagents *viz*., phloroglucinol, propionitrile, ether and $ZnCl_2$ must be in absolute dry condition so as to obtain better yield and purest product.

(3) HCl-Gas should be made dry before passing it into the reaction mixture in order to get a better yield of the intermediate salt.

4.7.6.1.7 Recrystallization. The product obtained is pure enough for many purposes, but may be further purified to an absolute pure state by recrystallization from minimum volume of hot water (approx. 35 ml per g) and drying as usual at 120°C, having mp 175-176°C and yield 29.0 g.

4.7.6.1.8 Theoretical Yield/Practical Yield. The theoretical yield may be calculated from the equation under theory (section 4.7.6.1.3) as given below :

126.11 g of Phloroglucinol on reacting with 55.08 g of Propionitrile

yields Flopropione = 182.18 g

$\therefore$ 25.2 g of Phloroglucinol shall yield Flopropione $= \frac{182.18}{126.11} \times 25.2 = 36.4$ g

Hence, Theoretical yield of Flopropione = **36.4 g**

Reported Practical yield = 30.5 g

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{30.5}{36.4} \times 100 =$ **83.79**

4.7.6.1.9 Physical Parameters. Flopropione is obtained as monohydrate needles from water. The anhydrous compound has mp 175-176°C. It is found to be soluble in ethanol, ether, ethyl acetate, hot water ; and very slightly soluble in cold water.

4.7.6.1.10 Uses. It is used as an antispasmodic.

4.7.6.1.11 Questions for *Viva-Voce*

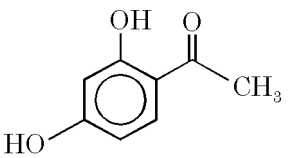
(1) Why is it required to carry out the Hoesch Reaction in an absolute anhydrous condition ?

(2) How would you prepare dry HCl-gas in the laboratory scale ? Can it be dried, if yes ; what is the procedure ?

(3) Why is it necessary to preserve the compound preferably in an anhydrous condition ?

4.7.6.2 Resacetophenone

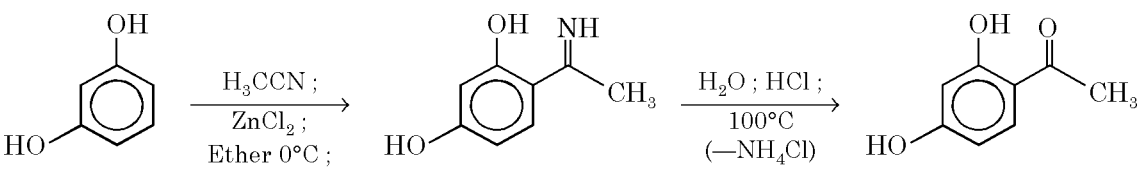
4.7.6.2.1 Chemical Structure



Resacetophenone

4.7.6.2.2 Synonyms. 1-(2,4-Dihydroxyphenyl) ethanone ; 2′, 4′-Dihydroxy-acetophenone.

4.7.6.2.3 Theory



Resorcinol (110.11) | Chlorozincate of Imine salt | Resacetophenone (152.15)

Resorcinol (a dihydric phenol) when reacted with acetonitrile (or methyl cyanide) in the presence of anhydrous zinc chloride in an ethereal medium at 0°C produces the chlorozincate of an '**Imine Salt**'. The resulting intermediate on subjecting to hydrolysis at almost 100°C knocks out a mole of NH_4Cl with the production of resacetophenone.

Important Note : It is mandatory for Hoesch Reaction to maintain absolute anhydrous conditions ; therefore, the ether and the acetonitrile must each be dried and distilled before using in the synthesis, and the resorcinol should also be dried in a vacuum desiccator.

4.7.6.2.4 Chemicals Required

Resorcinol : 5 g ; Acetonitrile : 3.5 ml ; Anhydrous Zinc chloride : 2 g ; Anhydrous sodium-dried Ether : 25 ml ; Dry Toluene : 50 ml.

4.7.6.2.5 Procedure

The following steps are to be followed in a sequential manner :

(1) Fit a 100 ml conical flask with a rubber stopper carrying a long inlet and a short outlet tubing ; the latter being connected to a *Calcium-Chloride-Guard-Tube*.

(2) Add sequentially 25 ml of ether, 5 g of resorcinol and 3.5 ml (2.8 g) of acetonitrile into the reaction flask.

(3) Rapidly pulverize 2 g of $ZnCl_2$ in a clean glass pestle and mortar (that should have been pre-heated in an oven at 80-90°C), and transfer the same to the reaction mixture in one-go ; finally stopper the conical flask.

(4) Now, clamp the flask securely in a water-bath charged with a freezing mixture (0°C) and pass a steady and rapid stream of dry HCl-gas (see the synthesis on Flopropione under section 4.7.6.1) into the reaction mixture while swirling the contents intermittently.

(5) Once the resulting mixture is saturated with HCl-gas (approx. 2 hours), close the inlet rubber tubing with a clip, and set the flask aside for 24 hours.

(6) Filter off the *chlorozincate of the imine i.e.*, the intermediate which has separated eventually, and wash the product with a little spray of ether on the filter paper in Büchner funnel.

(7) The hydrolysis is affected by adding the chlorozincate to 50 ml of dilute HCl (6 N), and subsequently boiling the mixture under reflux for a period of 30 minutes.

(8) Cool the clear solution, preferably in a refrigerator overnight, when the almost colourless crystals of the crude product resacetophenone separate out, filter it at the pump, wash with a little water, drain well and dry it in a desiccator over paraffin shavings.*

The yield of the creamy-coloured crystals is 4.2 g having mp 144-145.5°C.

4.7.6.2.6 Precautions

(1) All glass apparatus and the reagents used in this synthesis should be in perfectly dry condition to accomplish maximum yield and obviously a pure product quality.

(2) The HCl-gas should be made dry before using in this synthesis [see section 7.4.6.1.5. (2)].

4.7.6.2.7 Recrystallization. Dissolve the entire crude product in 50 ml of sodium-dried toluene, drain thoroughly and dry in a desiccator over paraffin shavings to obtain a creamy crystalline product 3.9 g mp 145-147°C.

4.7.6.2.8 Theoretical Yield/Practical Yield

The theoretical yield may be calculated from the equation under theory (section 4.7.6.2.3) as given below :

110.11 g of Resorcinol when reacted with acetonitrile

yields Resacetophenone = 152.15 g

$\therefore$ 5 g of Resorcinol shall yield Resacetophenone $= \frac{152.15}{110.11} \times 5 = 6.9$ g

Hence, Theoretical yield of Resacetophenone = **6.9 g**

Reported Practical yield = 4.2 g

*Compounds generally recrystallized from : Benzene, Toluene, Petrol etc., a few freshly cut shavings of clean paraffin wax must be added to the fused calcium chloride kept in the lower portion of the desiccator. The surface of the paraffin wax helps to absorb the vapours of organic solvent, specifically the hydrocarbons.

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{4.2}{6.9} \times 100 = \mathbf{60.86}$

4.7.6.2.9 Physical Parameters. Resacetophenone is obtained as needles or leaflets having mp 145-147°C. It is gradually decomposed by water ; soluble in pyridine, warm ethanol, glacial acetic acid ; and almost insoluble in benzene, chloroform and ether.

4.7.6.2.10 Uses

(1) It is invariably employed in a 10% (w/v) ethanolic solution as a reagent for testing Fe^{3+} in biological products.

(2) It is also used in carrying out the studies on the biotransformation of paeonol by means of isotope tracer techniques.

4.7.6.2.11 Questions for *Viva-Voce*

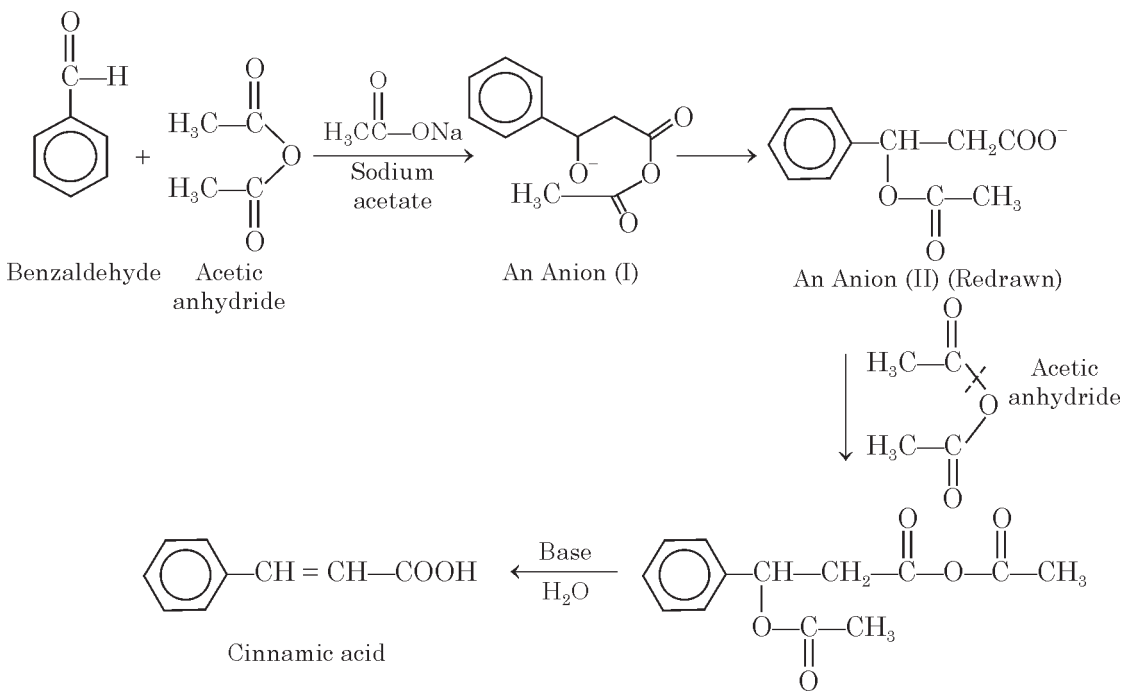
(1) Why is it necessary to employ dry reagents in Hoesch Reaction ?

(2) What is the underlying theory for the synthesis of Resacetophenone ?

(3) What is the role of '*paraffin shavings*' in dry a product finally as Resacetophenone ?

4.7.7 Perkin Reaction

The formation of α, β-unsaturated carboxylic acid by '*Aldol Condensation*', *viz*., of aromatic aldehydes and acid anhydrides in the presence of an alkali salt of the acid is known as the **Perkin Reaction.***

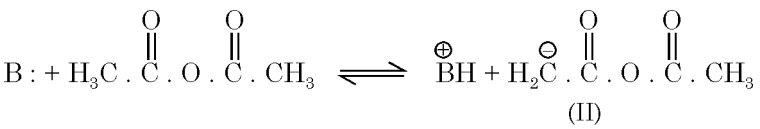


*Perkin, W.H. *J. Chem. Soc.*, **21**, 53, 181 (1868) ; Poonia *et al. Bull. Chem. Soc. Japan,* **53**, 3338 (1980) ; Rosen, T., *Comp. Org. Syn.*, **2**, 395-408 (1991).

The above discourse of the **Perkin Reaction** is self-explanatory in which benzaldehyde and acetic anhydride interacts to form an anion (I) that undergoes molecular rearrangement to give another anion (II). The resulting restructured anion (II) reacts with acetic anhydride to form an intermediate which subsequently undergoes hydrolysis in the presence of a base to give rise to the formation of an α, β-unsaturated carboxylic acid *i.e.,* cinnamic acid.

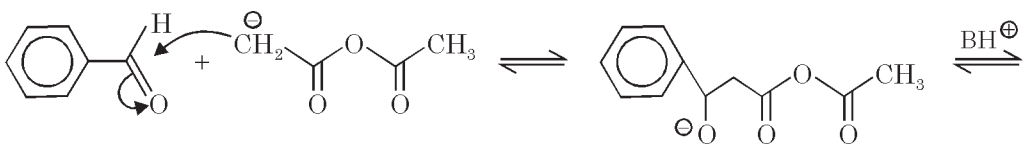
Mechanism of Perkin reaction. The mechanism of the reaction, which is of the aldol-type may be expatiated with the help of the following equations (*a*) and (*b*) respectively.

(*a*)

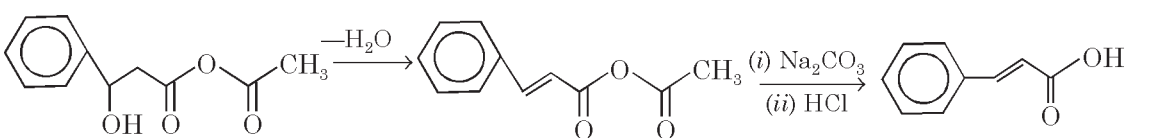


(II)

(*b*)



(I) (II) (III)

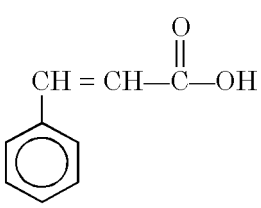


(IV) (V) (VI) + H_3COOH

The carbonyl function of the aromatic aldehyde (I) and an active methylene moiety of the anhydride (II) ; the function of the basic catalyst (acetate anion, $H_3C.COO^{\ominus}$, or triethylamine, $[(C_2H_5)_3N]$ is to form an anion (III), which in the presence of $\overset{\oplus}{B}H$ yields (IV). The resulting product (IV) loses a molecule of water to give an α, β-unsaturated anhydride (V) that ultimately undergoes hydrolysis in the presence of Na_2CO_3 and HCl to result into the formation of an α, β-unsaturated carboxylic acid (VI) and a mole of acetic acid.

4.7.7.1 Cinnamic Acid

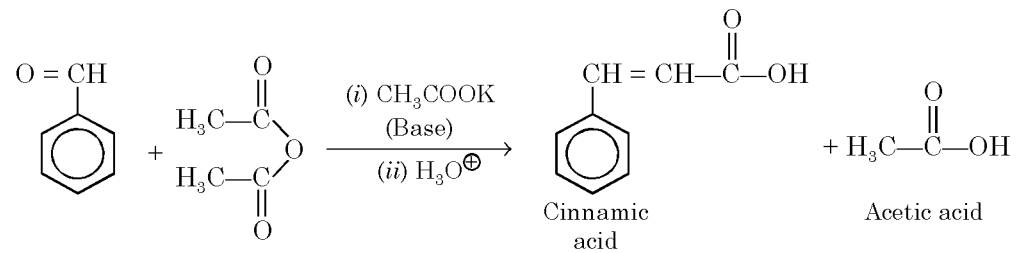
4.7.7.1.1. Chemical Structure



Cinnamic acid

4.7.7.1.2 Synonyms. 3-Phenyl-2-propenoic acid ; β-Phenylacrylic acid ;

4.7.7.1.3 Theory



The interaction between benzaldehyde (aromatic aldehyde) and acetic anhydride (an aliphatic anhydride capable of providing an '*active methylene*' moiety) in the presence of a basic catalyst, such as : acetate ion and a hydronium ion yields an α, β-unsaturated carboxylic acid, cinnamic acid, and a mole of acetic acid.

4.7.7.1.4 Chemicals Required. Pure redistilled Benzaldehyde : 10.5 g ; Fused and powdered Potassium acetate : 6 g ; Acetic Anhydride : 15 g ; Sodium carbonate : 20 g ; Conc. Hydrochloric Acid (12 N) : q.s. ; and Rectified Spirit : 50 ml.

4.7.7.1.5. Procedure. Following steps may be followed in a sequential order :

(1) Transfer carefully 10.5 g (10 ml, 0.2 mol) of freshly distilled pure benzaldehyde, 15 g (14 ml, 0.29 mol) of acetic anhydride together with 6 g (0.122 mol) of freshly fused and finely powdered potassium acetate in an absolutely dry 250 ml round-bottomed flask duly provided with $CaCl_2$-guard tube at its top-end.

[Note. Potassium acetate may be replaced with sodium acetate also, but in that case the reaction is appreciably slower and sluggish ; and a further heating for 3-4 hours is required and mandatory.

(2) Mix the contents of the RB-flask thoroughly and heat the reaction mixture in an oil bath maintained at 160°C for 60 minutes ; and further at an elevated temperature of 170-180°C for almost 3 hours.

(3) Pour the contents of the reaction flask while still hot (90°-100°C) into about 50 ml of water contained in a 500 ml round-bottomed flask that has been duly fitted for steam-distillation operation ; rinse the contents of the flask with a little hot water and pour it in the 500 ml RB-flask.

(4) Now, make the resulting solution in the 500 ml RB-flask alkaline (to litmus paper) by adding gradually a saturated solution of Na_2CO_3 with vigorous shaking until a drop of the liquid withdrawn on the tip of a glass rod turns red litmus to a distinct blue.

[Note : NaOH cannot be used (instead of Na_2CO_3) for affecting alkalinity, because it may produce BENZOIC ACID by the Cannizarro Reaction from the unchanged/unreacted portion of *Benzaldehyde.*]

(5) Subject the solution to steam-distillation meticulously until all the '*unreacted benzaldehyde*' is removed and the distillate is absolutely clear. Cool the contents of the distillation flask and filter at the suction pump to get rid of most resinous unwanted by-products.

(6) Carefully, render the filtrate to acidic pH by adding concentrated HCl gradually in small lots at intervals, and with vigorous continuous agitation until the evolution of CO_2 ceases completely.

(7) Chill the resulting solution when cinnamic acid gets separated as almost colourless crystals, filter in the Buchner funnel, wash with a little cold water, drain well with an inverted glass stopper, and dry at 100°C.

The yield of the crude product is 9.5 g having mp ranging between 131-132.5°C.

4.7.7.1.6 Precautions

(1) All reagents, namely : benzaldehyde, acetic anhydride and potassium acetate must be of very good quality and absolutely dry so as to accomplish reasonably purer end product with maximum yield.

(2) Make the reaction mixture distinctly alkaline prior to the removal of '*Benzaldehyde*' (unreacted) by steam-distillation.

(3) The resulting reaction mixture is cooled and acidified cautiously to litmus paper when the desired product *i.e.*, cinnamic acid is knocked out in an acidic medium.

4.7.7.1.7 Recrystallization. The crude product may be recrystallized either from a mixture of water and rectified spirit (3 : 1) or from hot water. The yield of pure recrystallized product is 9.1 g, mp 132-133°C.

4.7.7.1.8 Theoretical Yield/Practical Yield. The theoretical yield is calculated from the equation under theory (section 4.7.7.1.3) as given under :

106.12 g of Benzaldehyde on reacting with 102.09 g of Acetic Anhydride yields Cinnamic Acid = 148.16 g

$\therefore$ 10.5 g of Benzaldehyde shall yield Cinnamic Acid $= \frac{148.16}{106.12} \times 10.5 = 14.66$ g

Hence, Theoretical yield of Cinnamic Acid = **14.66 g**

Reported Practical yield = 9.5 g

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{9.5}{14.66} \times 100 =$ **64.8**

4.7.7.1.9 Physical Parameters. Cinnamic acid is obtained as monoclinic crystals having mp 133°C ; d_4^4 1.2475 ; bp 300°C ; K at 25° = 3.5×10^{-5} ; uv_{max} (ethanol) : 273 nm. Its solubility profile is as follows : 1 g dissolves in 2L water at 25°C (more soluble in hot water) ; in 6 ml ethanol ; 5 ml methanol ; 12 ml chloroform ; and almost freely soluble in benzene, ether, acetone, glacial acetic acid, carbon disulphide and oils. The alkali salts are observed to be soluble in water.

The *pmr* and *ms* spectral studies of pure recrystallized cinnamic acid evidently shows the following characteristic peaks and fragmentation modes :

pmr-Spectrum ($CDCl_3$, TMS). It shows signals at δ 6.41 (*d*, 1H, $= CH.\overset{\overset{O}{\|}}{C}—O$) ; 7.73(*d*, 1H, $C_6H_5 - CH$) ; 7.17 – 7.69 (*m*, 5H, CAR–H) and 11.90 (*s*, 1H, COOH).

ms-Spectrum. It reveals the principal fragment ions at *m/z* 148 (M) ; 147 (M–H) ; 131 (M–OH) ; 130 (M–H_2O), 103 (M–COOH) ; 102 (130–CO_2) ; 77 (103–C_2H_2) ; and 51 (77–C_2H_2).

4.7.7.1.10 Uses

(1) A few typical esters of cinnamic acid, for instance ; chaulmoogryl and other derivatives are used in medicine exclusively.

(2) The main use of cinnamic acid is in the manufacture of the methyl, ethyl and benzyl esters for the perfume industry.

(3) The '*ethyl ester*' is used importantly in preparing sophisticated glass lenses and prisms that form a vital component in designing the 'optics' in various analytical equipments for the Quality Assurance Laboratories in testing drug substances.

4.7.7.1.11 Questions for *Viva-Voce*

(1) Why potassium acetate is preferred over sodium acetate in carrying out the synthesis of cinnamic acid by the Perkin Reaction ?

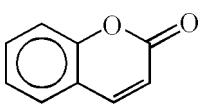
(2) Why do we use Na_2CO_3 and not NaOH in rendering the reaction mixture '**alkaline**' prior to the removal of unreacted Banzaldehyde by steam-distillation ?

(3) How would you identify Cinnamic Acid by *pmr*-spectrum obtained in $CDCl_3$ using TMS-as a reference standard ?

(4) What does the peak *m/z* 148(M) in *ms*-Spectrum of cinnamic acid reveals ?

4.7.7.2 Coumarin

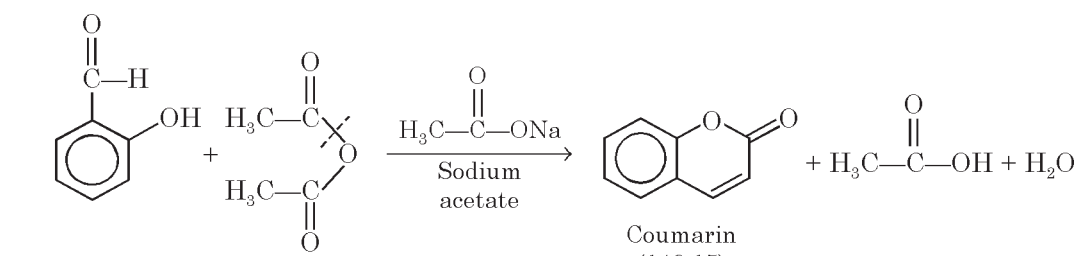
4.7.7.2.1 Chemical Structure



Coumarin

4.7.7.2.2 Synonyms. 1, 2-Benzopyrone ; 2H-1-Benzopyran-2-one ; *cis-o*-Coumarinic acid lactone ; Cumarin ; Coumarinic anhydride ; Tonka bean Camphor ;

4.7.7.2.3 Theory



Salicylaldehyde (122.12) | Acetic anhydride (102.09) | Coumarin (146.15)

The interaction between benzaldehyde and acetic anhydride in the presence of sodium acetate results into the formation of the heterocyclic pyran ring to give coumanin in addition to a mole each of acetic acid and water as products of reaction.

4.7.7.2.4 Chemicals Required. Salicylaldehyde : 8 g ; Acetic Anhydride : 20 ml ; Fused and finely powdered Sodium Acetate : 10 g ; Sodium Carbonate : q.s. ; and Activated Animal Charcoal : 2 g ;

4.7.7.2.5 Procedure. The following steps may be adopted in a methodical manner as stated under :

(1) Transfer 8 g salicylaldehyde, 10 g fused sodium accetate and 20 ml acetic anhydride in a 250 ml round-bottomed flask duly installed with an air reflux condenser the top-end of which should be provided with a $CaCl_2$-guard tube.

(2) Heat the mixture in an oil-bath for a duration of 6 hours between 180-190°C.

(3) Cool the contents of the flask and subject it to steam distillation, so as to get rid of the unreacted salicylaldehyde completely, and discard the distillate.

(4) Add to the resulting residue in the flask solid Na_2CO_3 slowly and carefully until the solution is rendered alkaline to litmus paper.

(5) Chill the contents of the flask in an ice-bath when the desired product coumarin gets separated. Filter it in a Büchner funnel, wash with a little spray of cold water, drain well and dry it in filter paper folds.

The yield of the crude product is 4.3 g mp 68–69°C.

4.7.7.2.6 Precautions

(1) Always use freshly fused and finely powdered sodium acetate in the Perkin Reaction.

(2) The heating of the reaction mixture in an oil-bath should be steady and gentle for a period of 6 hours at a stretch preferably.

(3) After removal of the unreacted salicylaldehyde by steam distillation the residual product must be made alkaline carefully by adding solid Na_2CO_3 to litmus paper.

(4) A small amount of activated decolourizing carbon powder may be used while recrystallizing the crude product.

4.7.7.2.7 Recrystallization. Dissolve the crude coumarin in 250-300 ml of boiling water and add to it 1-1.5 g of decolourizing carbon. Filter at the pump and concentrate the filtrate over a water bath till its volume becomes almost 1/3 rd its original volume. Keep it in the refrigerator overnight when beautiful crystals of pure coumarin shall separate out.

The yield of the pure coumarin is 4.0 g mp 68.5-70°C.

4.7.7.2.8 Theoretical Yield/Practical Yield

The theoretical yield is calculated from the equation under theory (section 4.7.7.2.3) as given below :

122.12 g of Salicylaldehyde on reacting with 102.09 g of Acetic Anhydride yields Coumarin = 146.15 g

$\therefore$ 8 g of Salicylaldehyde shall yield Coumarin $= \dfrac{146.15}{122.12} \times 8 = 9.57$ g

Hence, Theoretical yield of Coumarin = **9.57 g**

Reported Pactical yield = 4.3 g

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{4.3}{9.57} \times 100 = \mathbf{44.93}$

4.7.7.2.9 Physical Parameters. Coumarin is invariably obtained as orthorhombic, rectangular plates having a pleasant, fragrant smell resembling that of vanilla beans. It has a burning taste, mp 68-70°C, bp 297-299°C. 1 g of Coumarin is found to dissolve in 400 ml of cold water, 50 ml of boiling water, freely soluble in ethanol, chloroform, ether, oils ; and also soluble in alkali hydroxide solutions (*e.g.*, NaOH, KOH etc.)

4.7.7.2.10 Uses

(1) It is used mostly as a flavouring agent in pharmaceutical preparations *i.e.*, as a pharmaceutical aid.

(2) Many structural analogues of 'coumarin' may be employed as anticoagulants.

4.7.7.2.11 Question for *Viva-Voce*

(1) What is the general and most important usage of natural coumarins *i.e.*, **dicumarol** in medicine ?

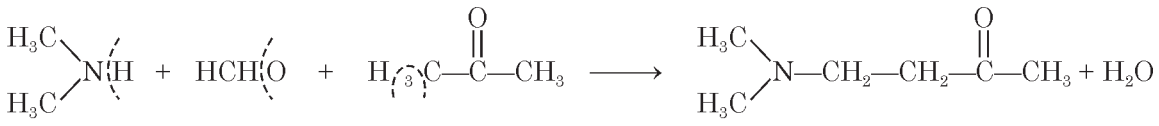
(2) Why is it necessary to use perfectly dry reagents in Perkin Reaction ?

(3) How do we remove the unreacted salicylaldehyde from the reaction mixture ?

(4) Why is coumarin soluble in solutions of alkali hydroxide ?

4.7.8 Mannich Reaction

The reaction of compounds having an active hydrogen atom with non-enolizable aldehydes and ammonia or primary or secondary amines to give rise to the formation of aminomethylated product exclusively is commonly known as the **Mannich Reaction**; and the product is invariably termed as the **Mannich Base**, as depicted below :



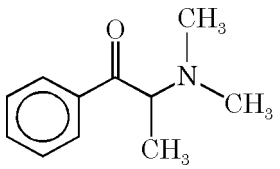
Dimethyl amine — Formaldehyde — Acetone — N, N-Dimethylaminoethyl methyl ketone (An aminomethylated product)

Explanation. The active H-atom of the methyl function in acetone, the H-atom of the secondary amine (dimethy amine) and the O-atom of the aldehyde (formaldehyde) gets eliminated as one mole of water. Thus, the resulting aminomethylated product essentially possesses an additional methylene (—CH_2—) moiety. In other words, in all Mannich reactions the carbon-chain shall be increased by **one** due to the —CH_2— methylene function forming a part of the Mannich Base.

In general, the Mannich bases are scantly water soluble ; therefore, they are mostly employed as their respective hydrochlorides which are fairly water soluble.

4.7.8.1 Metamfepramone

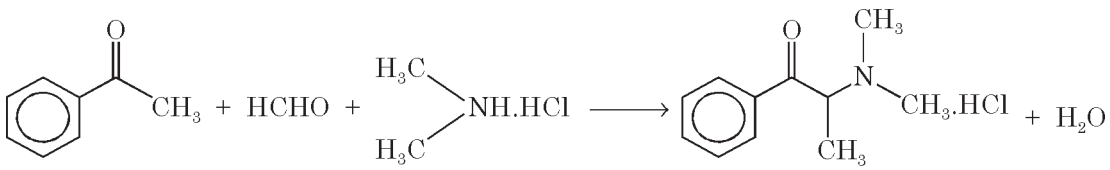
4.7.8.1.1 Chemical structure



Metamfepramone

4.7.8.1.2 Synonyms. 2-(Dimethylamino) propiophenone ; 2-(Dimethylamino)-1-phenyl-propanone ; N-Methylephedrone ; Dimepropion ; α-(Dimethylamino) propiophenone ; Benzoyl-α-dimethyl-amino ethane.

4.7.8.1.3 Theory



Acetophenone (120.15)	Paraformal-dehyde	Dimethylamine hydrochloride (81.58)	Metamfepramone hydrochloride [salt] (213.75)

Acetophenone reacts with dimethylamine hydrochloride along with one mole of formaldehyde (obtained from **paraformaldehyde** which is polymerized formaldehyde) to yield the corresponding salt metamfepramone hydrochloride plus a mole of water. Most of the Mannich reactions, it is a practice to make use of the hydrochloride salt of the secondary amine, so that the reaction moves faster in the solubilized conditions ; and the resulting condensed product, with an additional methylene linkage (—CH_2—) is also obtained as its HCL salt.

4.7.8.1.4 Chemicals Required. Dimethylamine hydrochloride : 6.6 g ; Paraformaldehyde : 2.5 g ; Acetophenone : 7.5 ml ; Acetone : 75 ml ; Rectified spirit : 25 ml ; Ethanol : 10 ml.

4.7.8.1.5 Procedure. The various steps followed are as given below :

(1) Transfer 6.6 g dimethylamine hydrochloride, 2.5 g paraformaldehyde, and 7.5 ml acetophenone into a 250 ml round-bottom flask fitted with a reflux condenser.

(2) Add to the flask 10 ml of ethanol and a few drops of acetophenone, and shake the contents thoroughly.

(3) Reflux the reaction mixture on an electric water bath for a duration of 2 hours until it becomes perfectly clear and homogeneous. In case, any residue still appears, filter it and discard the same.

(4) Add to the resulting clear filtrate 50 ml acetone and keep it in a refrigerator overnight when the salt of the Mannich base *i.e.,* metamfepramone hydrochloride gets separated.

(5) Filter the solid residue in a Büchner funnel under suction, wash with a spray of 4–5 ml acetone and dry in the folds of filter paper.

The yield of the crude product is 9.7 g having mp ranging between 201–203°C.

4.7.8.1.6 Precautions

(1) All the reagents used in the condensation Mannich reaction should be preferably free from any moisture, whatsoever.

(2) After refluxing the reaction mixture for 2 hours, any solid residue appearing must be discarded immediately by simple filtration under suction.

(3) The product may be either air dried or within the folds of filter paper conveniently.

4.7.8.1.7 Recrystallization. The crude product may be recrystallized by dissolving the same in minimum quantity of a mixture of rectified spirit and acetone (1 : 5) when pure metamfepramone hydrochloride is obtained as crystals having mp 202–204°C and yield 9.3 g.

4.7.8.1.8 Theoretical Yield/Practical Yield. The theoretical yield is calculated from the equation under theory (section 4.7.8.1.3) as follows :

120.15 g of Acetophenone on interacting with 81.58 g of Dimethylamine hydrochloride yields Metamfepramone HCl = 213.75 g

$\therefore$ 7.75 g* of Acetophenone shall yield Metamfepramone HCl

$$= \frac{213.75}{120.15} \times 7.75 = 13.79\text{g}$$

Hence, Theoretical yield of Metamfepramone HCl = **13.79 g**

Reported Practical yield = 9.7 g

Therefore, Percentage Practical yield

$$= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

$$= \frac{9.70}{13.79} \times 100 = \mathbf{70.34}$$

4.7.8.1.9 Physical Parameters. The recemic mixture of metamfepramone hydrochloride is obtained as crystals having mp 202–204°C.

4.7.8.1.10 Uses

(1) It is reported to be a sympathomimetic agent used as the hydrochloride in the treatment of *hypotension.*

(2) It is also employed in preparations for the relief of the symptoms of the *common cold.*

(3) It was *formerly* used as an *anorectic agent***.

4.7.8.1.11 Questions for *Viva-Voce*

(1) What is Mannich Reaction ?

(2) Why is it necessary to have a reactive hydrogen atom in a compound to undergo Mannich Reaction ?

(3) Why do we use 'Paraformaldehyde' preferably in a Mannich Reaction ?

(4) How does the 'Mannich Base' acquire an additional methylene linkage ? Explain.

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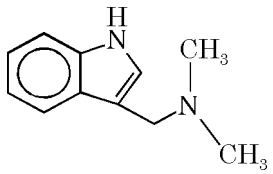
* The d_{15}^{15} of Acetophenone is 1.033.

** **Anorectic Agent.** An agent that decreases the appetite appreciably.

4.7.8.2 Gramine*

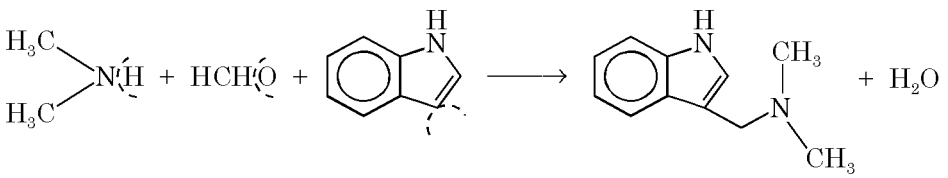
4.7.8.2.1 Chemical Structure



Gramine

4.7.8.2.2 Synonyms. Dimethylaminomethylindole ; Donaxine ; N, N-Dimethyl-1 H-indole-3-methanamine.

4.7.8.2.3 Theory



Dimethyl amine (45.08)	Formaldehyde	Indole (117.15)	Gramine (174.25)

The interaction between dimethylamine (a secondary amine) with indole in the presence of formaldehyde gives rise to the Mannich base gramine with the elimination of one mole of water as indicated in the above reaction. The shiny crystals of the alkaloid are obtained in a fairly pure state.

4.7.8.2.4 Chemicals Required. Aqueous Dimethylamine solution [25% (w/v)] : 21.25 ml ; Acetic Acid : 15 g ; Formaldehyde solution (37%) : 8.6 g ; Indole : 11.7 g ; Acetone : 60 ml ; Hexane : 60 ml ; KOH : 20 g.

4.7.8.2.5 Procedure. The various steps involved are as stated below :

(1) First of all, cool 21.25 ml (0.236 mol) of aqueous dimethylamine solution taken in a 100 ml flask in an ice bath (with freezing mixture), add 15 g of chilled acetic acid, immediately followed by 8.6 g (0.21 mol) of previously cooled formaldehyde solution.

(2) Transfer the entire contents of the flask in one lot on to 11.7 g indole (0.2 mol) ; use 10 ml of water so as to rinse the flask.

(3) The reaction mixture in the flask is allowed to attain room temperature, with intermittent swirling as the indole gets dissolved.

(4) Maintain the resulting solution between 30–40°C for nearly 24 hours ; and then pour it, with constant vigorous stirring, directly into a solution of 20 g of KOH in 150 ml of water. The crystals of *'garmine'* start separating out.

(5) Cool the contents in an ice bath for 2 hours and collect the crystals in a Büchner funnel under suction, wash with 2 to 3 successive 25 ml portions of ice-cold water, drain properly and finally dry to constant weight at 60°C.

---

* It is also found in rhizomes of *Arundo donax* Linn (family : *Graminae*).

The yield of the crude product is 16.8 g mp 131–133°C.

4.7.8.2.6 Precautions

(1) All the reactants are to be mixed at nearly 0°C, only then the mixture should be allowed to attain room temperature slowly.

(2) It is necessary to maintain the reaction mixture at 30–40°C for 24 hours so as to maximise the Mannich reaction.

(3) Gramine being alkaline in nature (an alkaloid) gets separated only in an alkaline medium using KOH solution.

4.7.8.2.7 Recrystallization. The crude product may be recrystallized from a mixture of acetone-hexane (1 : 1) ; and the crystals dried to a constant weight in an oven maintained at 60°C.

The yield of the pure product is 16.5 g having mp 133–134°C.

4.7.8.2.8 Theoretical Yield/Practical Yield. The theoretical yield is calculated from the equation given under theory (section 4.7.8.2.3) as stated below :

45.08 g of Dimethylamine on reacting with 117.15 g of Indole

yields Gramine = 174.25 g

$\therefore$ 5.31 g of Dimethylamine shall yield Gramine $= \frac{174.25}{45.08} \times 5.31 = 20.53$ g

Hence, Theoretical yield of Gramine = **20.53 g**

Reported Practical yield = 16.8 g

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{16.8}{20.53} \times 100 =$ **81.83**

4.7.8.2.9 Physical Parameters. Gramine is mostly obtained as shiny, flat needles or plates from acetone having mp 138–139°C. It is found to be soluble in ethanol, ether, chloroform ; slightly soluble in cold acetone ; and almost insoluble in water and petroleum ether.

4.7.8.2.10 Uses

(1) It has been observed that *gramine hydrochloride* helps to raise blood pressure.

(2) It also contracts the isolated intestine and uterus of rabbits.

(3) Its action is quite identical to that of *d*-pseudo ephedrine.

(4) It is reported to be an insect-feeding inhibitor.

4.7.8.2.11 Questions for *Viva-Voce*

(1) Is donaxine an alkaloid found in plants ?

(2) How does a mole of water gets knocked out in a Mannich reaction ? Explain.

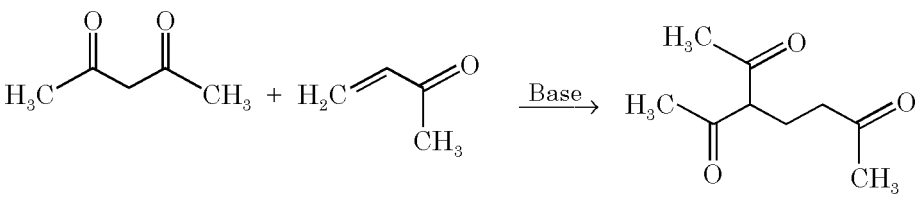
(3) Why is C-3 position in the indole nucleus more vulnerable to attack by the incoming attachments ? Explain.

(4) How does **'gramine'** form a salt with a mineral acid like hydrochloric acid ?

4.7.9 Michael Reaction* (Addition, Condensation)

In general, the addition of active methylene compounds to the double bond of α, β-unsaturated *esters, ketones* etc., in the presence of particularly the basic catalysts is termed as the *Michael Reaction.*

In other words, the base-promoted conjugate addition of carbon nucleotides (donors) to activated unsaturated systems (acceptors) is invariably known as the *Michael Reaction*, as indicated below :



Donor Acceptor

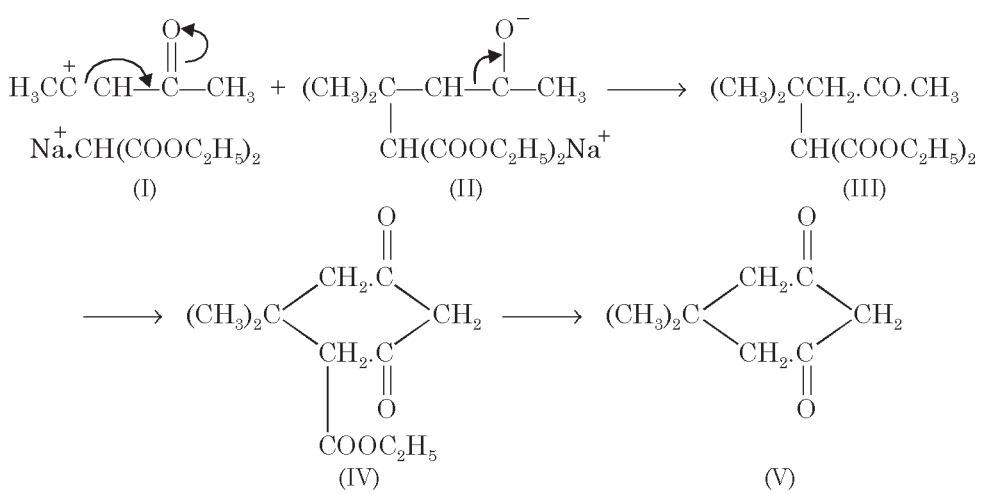
There are a number of specific *donor, acceptor* and *base* that are frequently employed in the *Michael Reaction*, namely :

Donors. Malonates ; Cyanoacetates ; Carboxylic Esters ; Ketones ; Aldehydes ; Nitriles ; Nitro compounds ; and Sulphones.

Acceptors. α, β-Unsaturated ketones ; Esters ; Aldehydes, Amides ; Carboxylic acids ; Nitriles ; Sulphoxides ; Phosphonates ; and Phosphoranes.

Bases. $NaOC_2H_5$ (Sodium Ethoxide) ; HN $(C_2H_5)_2$ (Diethylamine) ; KOH (Potassium Hydroxide) ; KOC $(CH_3)_3$ (Potassium *tertiary-Butoxide*) ; N $(C_2H_5)_3$ (Triethylamine) ; NaH (Sodium Hydride).

Mechanism of Michael Reaction



* Michael, A, *J. Pract, Chem.,* [2] **35**, 349 (1887) ; J. d' Angelo *et. al. Tetrahedron Asymmetry*, **3**, 459–505 (1992) ; Oare, C, *et. al. Top Stereochem.* **20,** 87-170, (1991).

The various steps involved are as enumerated below :

(1) The addition of the Sodio-derivative of ethyl acetoacetate, ethyl malonate, or ethyl cyano acetate to an *'olefine function'* that is specifically activated by a keto, nitrile or ester $\left(\begin{array}{l}\text{O}\\ \|\\ \text{.C—OR}\end{array}\right)$ moiety.

(2) The addition of diethyl sodio-malonate to **mesityl oxide (I),** can be viewed more or less as an *'addition'* to give rise to the formation of the **anion (II)**.

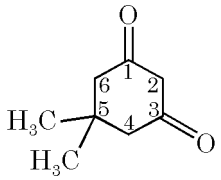
(3) The resulting anion (II), on subsequent *'acidification'* yields the corresponding *ester (III)* having the *'keto function'* regenerated.

(4) The ester (III) may, however, get rid of one mole of ethanol by means of an internal **'Claisen-ester condensation'** to form the respective **cyclohexane derivative** (IV).

(5) Thus, the resulting cyclohexane derivative (IV) *i.e.,* the ester of a **'β-keto acid'**, undergoes **two** chemical changes in quick succession, namely : (*a*) *hydrolysis,* and (*b*) *decarboxylation*, to form **5, 5-dimethyl-cyclohexan-1, 3-dione (V)** or **'Dimedone'**.

4.7.9.1 5, 5-Dimethyl-1, 3-Cyclohexanedione (or Dimedone)

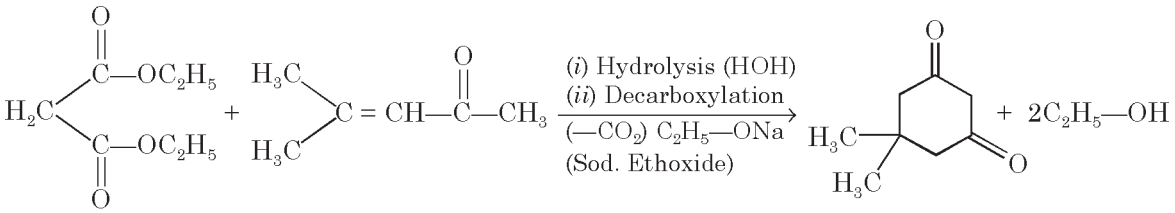
4.7.9.1.1 Chemical Structure



5, 5-Dimethyl-1, 3-cyclohexanedione

4.7.9.1.2 Synonyms. 1, 1-Dimethyl-3, 5-diketocyclohexane ; 1, 1-Dimethyl-3, 5-cyclohexanedione ; Dimethyldihydroresorcinol ; Dimedone ; Methone.

4.7.9.1.3 Theory



Ethyl malonate (160) | Mesityl oxide (98.14) | Dimedone (140.18)

Ethyl malonate and mesityl oxide interacts in the presence of freshly prepared sodium ethoxide when two reactions take place almost simultaneously *viz.,* hydrolysis and decarboxylation thereby undergoing cyclization to form dimedone and two moles of ethanol are eliminated.

4.7.9.1.4 Chemicals Required. Absolute ethanol : 40 ml ; Freshly cut Sodium Metal : 2.3 g ; Ethyl Malonate (pure) : 17 g ; Mesityl oxide : 10.2 g ; Sodium Hydroxide : 10 g ; Petroleum Ether (bp 60–80°C) : 40 ml ; Acetone : 40 ml ; Dilute HCl (6N) : 100 ml.

4.7.9.1.5 Procedure. The steps involved in the synthesis are described below sequentially :

(1) First of all set up a 250 ml three-necked flask adequately fitted with a mechanical variable-speed stirrer, a double-reflux condenser and a dropping funnel.

(2) Transfer 40 ml of absolute ethanol in the flask, and then add carefully freshly cut small pieces of sodium metal into it.

(3) Immediate effervescence of nescent hydrogen will commence and the pieces of sodium metal start getting dissolved.

(4) Heat the resulting solution on a pre-heated electric water bath. Introduce first 17 g (17 ml) of pure ethyl malonate into the reaction flask, followed by gradual addition of 10.2 g (12 ml) mesityl oxide.

(5) The resulting mixture will turn into a thick and viscous slurry. Boil the slurry under reflux for at least 60 minutes with constant mechanical stirring. Now, add a solution of 10 g of NaOH pellets dissolved in 50 ml of water. Continue boiling the pale-yellow solution for a further duration of 90–100 minutes gently.

(6) While the solution is still hot, add dilute HCl (6 N) very cautiously until the stirred solution is just acidic to litmus.

(7) Distil off the maximum possible amount of ethanol using the same electric-water-bath. **(Caution : Ethanol is highly inflammable solvent).**

(8) Add again more of dilute HCl (6 N) to the residual hot solution until it is just acidic to **methyl orange*** indicator. The desired product dimedone gets separated as an *oily liquid* which solidifies on cooling. Filter the product in a Büchner funnel under suction, wash it with a little ice-cold water, and dry it in a vacuum desiccator.

The yield of the pale-cream coloured crystals is 12.2 g having mp 139–144°C (with preliminary softening).

4.7.9.1.6 Precautions

(1) The sodium ethoxide must be prepared in a perfectly dry flask using **absolute ethanol** and freshly cut pieces of sodium metal.

(2) The addition of requisite quantity of mesityl oxide into the reaction mixture must be done in small lots at intervals with vagorous stirring.

(3) The unreacted ethanol has to be distilled off completely before making the reaction mixture acidic to methyl orange with dilute HCl (6 N).

4.7.9.1.7 Recrystallization. The crude product is recrystallized from a mixture of equal volumes of petroleum ether (bp 60–80°C) and acetone, thereby obtaining almost colourless crystals upto 11.8 g, mp 148–149.5°C.

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* **Methyl Orange.** pH 3.1 *red* ; pH 4.4 *yellow ;* colour change *yellow* to *red*.

4.7.9.1.8 Theoretical yield/Practical yield. The theoretical yield may be calculated from the equation given under theory (section 4.7.9.1.3) as given under :

160 g of Ethyl Malonate on reacting with 98.14 g of

Mesityl oxide yields Dimedone = 140.18 g

$\therefore$ 17 g of Ethyl Malonate shall yield Dimedone $= \frac{140.18}{160} \times 17 = 14.89$ g

Hence, Theoretical yield of Dimedone = **14.89 g**

Reported Practical yield = 12.2 g

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{12.2}{14.89} \times 100 =$ **81.93**

4.7.9.1.9 Physical Parameters. Dimedone is obtained as needles from water ; and as prisms from ethanol + ether. It melts at 148–150°C (decomposes). It is monobasic in water, having dissociation constant pK (25°C) : 5.15. Its dipole moment is 3.46. It is found to be soluble in methanol, ethanol, benzene, chloroform, acetic acid, and in 50% ethanol-water mixture.

4.7.9.1.10 Uses

(1) It is used invariably for the separation of aldehydes and ketones in natural medicinal products.

(2) It clearly differentiates between aldehydes and ketones by forming insoluble condensation products with the former, but not with the latter.

4.7.9.1.11 Questions for *Viva-Voce*

(1) What is Michael Reaction ?

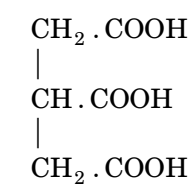
(2) What are the various types of donors, acceptors and bases usually employed in Michael reaction ?

(3) Why is it always recommended to use freshely prepared soldium ethoxide in synthesis ?

(4) Why is dimedone separated in an acidic medium at pH 3.1 of methyl orange ?

4.7.9.2 Tricarballylic Acid

4.7.9.2.1 Chemical Structure



Tricarballylic acid

4.7.9.2.2 Synonyms. β-Carboxyglutaric acid ; 1, 2, 3-Propane-tricarboxylic acid.

4.7.9.2.3 Theory. The synthesis of tricarballylic acid is usually accomplished by means of the following **three** steps, namely :

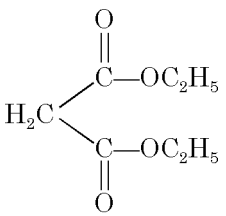
(*a*) Preparation of Diethylmalonate,

(*b*) Preparation of Ethylpropane-1, 1, 2, 3-Tetracarboxylate (Michael Reaction), and

(*c*) Preparation of Tricarballylic Acid.

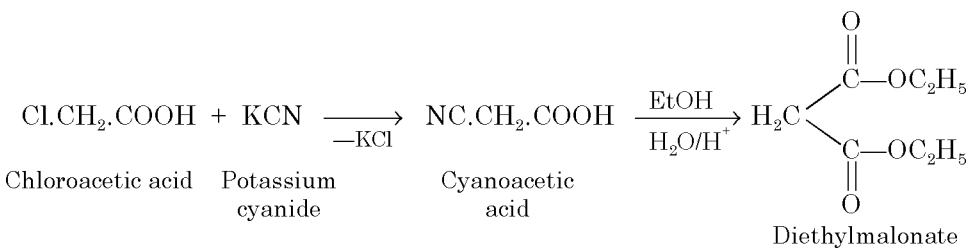
Step-I. Diethylmalonate

1. Chemical Structure



Diethylmalonate

2. Theory



The interaction between chloroacetic acid and potassium cyanide* yields cyanoacetic acid with the loss of one mole of KCl. The resulting acid on being reacted with ethanol in an acidic medium yields the corresponding diethyl malonate.

Mechanism. The nitrile function (or cyano moiety) in cyanoacetic acid undergoes hydrolysis to result into the formation of a carboxylic group *i.e.,* malonic acid, which upon esterification with EtOH forms the corresponding diethylmalonate.

3. Chemicals Required. Chloroacetic acid : 10 g ; Pure Sodium Bicarbonate : 9 g ; Potassium Cynanide (CAUTION) : 8 g ; Absolute Ethyl Alcohol : 20 ml ; Solvent Ether : q.s. ; concentrated H_2SO_4 (36 N) : 16 ml.

4. **Procedure :** The different steps are as given under :

(1) Dissolve 10 g chloroacetic acid in 20 ml water in a porcelain dish, and warm this to 50–55°C on a water bath with frequent stirring with a glass rod.

(2) To this warm solution add 9 g of pure solid sodium bicarbonate carefully in small lots at intervals with frequent stirring until the effervescence due to evolution of CO_2 gas ceases completely.

(3) Add catiously 8 g of potassium cyanide to the resulting solution, stir well and evaporate the mixture to a solid mass with continuous stirring with a glass rod at 130 ± 2°C.

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* **Potassium Cyanide (KCN).** It is a deadly poison ; therefore, it must be handled with extreme precaution using heavy duty rubber-gloves.

(4) Cool and break the solidified mass into small lumps and transfer it to a 250 ml round bottom flask fitted with a reflux condenser. To this incorporate 20 ml of absolute ethanol in small amounts through the condenser and then transfer slowly 16 ml sulphuric acid (36 N).

(5) Reflux the reaction mixture on a water bath for 60 minutes, cool the contents and add 20 ml water. Filter and wash the residue with 8 ml ether, shake the filtrate and separate the ethereal layer in a separating funnel. Extract the aqueous layer with 10 ml of ether each time **thrice.** Combine the ethereal layer and shake it thoroughly with concentrated sodium bicarbonate solution. Separate and dry the ethereal layer over absolutely anhydrous magnesium sulphate.

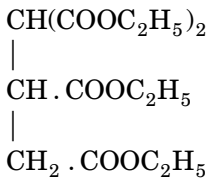
(6) First distil off the ether on a water bath, and subsequently distil the diethyl malonate under vacuo at 92–94°C and 16 mm Hg.

The yield of diethylmalonate is 10.6 g bp 197.5–199°C.

Note : *The diethylmalonate obtained in step-I is pure enough, and hence may be used in the next step-II without further purification.*

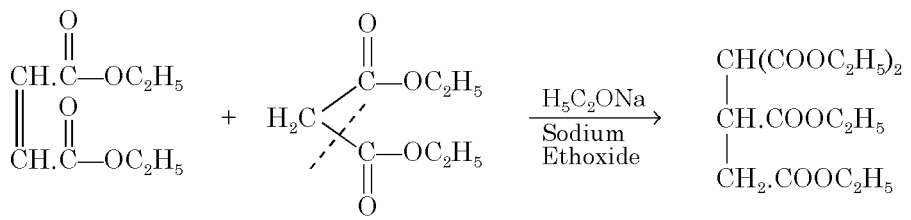
Setp-II. Ethylpropane-1, 1, 2, 3-tetracarboxylate

1. Chemical Structure



Ethylpropane-1, 1, 2, 3-tetracarboxylate

2. Theory



Diethyl fumarate + Diethylmalonate → Ethylpropane-1, 1, 2, 3-tetracarboxylate

A mole each of diethyl fumarate and diethylmalonate reacts together in the presence of freshly prepared sodium ethoxide to result into the formation of ethylpropane-1, 1, 2, 3-tetracarboxylate. In fact, diethylmalonate gets split up as shown above by the dotted line, the double bond in diethyl fumarate changes into a single covalent bond ; thereby the residual, $—CH_2—\overset{\overset{O}{\|}}{C}—OC_2H_5$, hooks on to form the third C-chain, while the first C-atom gets an additional $—COOC_2H_5$ moiety.

3. Chemicals Required. Diethyl malonate (from Step-I) : 8 g (or 7.5 ml) ; Diethyl fumarate* : 7 g (or 6.5 ml) ; Absolute Ethanol : 13 ml ; Freshly cut pieces of Na-metal : 0.9 g ; Glacial acetic acid : 2.5 ml ; Carbon Tetrachloride : 10 ml.

4. **Procedure.** The various steps are stated as under :

(1) Dissolve 0.9 g freshly cut clean pieces of sodium metal in 13 ml absolute ethanol in a 100 ml dry round bottom flask fitted with a quick-fit double surface reflux condenser ; and add 7.5 ml diethyl malonate through the condenser.

(2) Warm the resulting reaction mixture very gently on a pre-heated electric water bath, and transfer 6.5 ml diethyl fumarate gradually so that the mixture continues boiling in a steady manner.

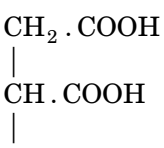
(3) Once the whole quantity of diethyl fumarate has been added, reflux the contents of the flask gently for a period of 60 minutes, cool and add 2.5 ml glacial acetic acid.

(4) Distil off the ethanol and to the remaining residue add 10 ml water. Shake and separate the *ester layer*. Extract the aqueous layer with three successive portions, 10 ml each, carbon tetrachloride and combine it with the first collected *'ester-layer'*.

(5) Distil off the carbon tetrachloride first at the atmospheric pressure (bp 76.7°C) completely ; and subsequently distil the ester under vacuo when pure ethylpropane-1, 1, 2, 3-tetracarboxylate gets distilled at 182–184°C/8 mm with a yield of 12.4 g.

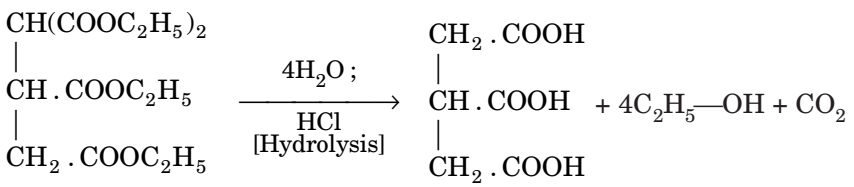
Step-III. Tricarballylic Acid

1. Chemical Structure



Tricarballylic Acid

2. Theory



Ethylpropane-1, 1, 2, 3-tetracarboxylate — Tricarballylic Acid

One mole of ethylpropane-1, 1, 2, 3-tetracarboxylate undergoes hydrolysis in the presence of HCl to yield one mole of the desired product tricarballylic acid, four moles of ethanol, and the elimination of one mole of CO_2 as a gas.

3. Chemicals Required. Ethylpropane-1, 1, 2, 3-tetracarboxylate (from Step-II) : 11 g ; Hydrochloric Acid (6 N) : 12 ml.

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* **Diethyl Fumarate.** It may be prepared by refluxing a mixture of 7 g fumaric acid, 12 ml absolute ethanol, 25 ml dry benzene along with 1 ml of concentrated sulphuric acid for a period of 12 hours at a stretch. The benzene layer is separated, dried and distilled at 213–215°C to obtain ultimately the pure diethyl fumarate 7.5 g.

4. Procedure. The steps adopted in the synthesis are as follows :

(1) Mix 11g ethylpropane-1, 1, 2, 3- tetracarboxylate with 12 ml of dilute hydrochloric acid (6N) in a 100 ml round botton flask adequately fitted with a long air condenser.

(2) Gently reflux the mixture for about 10-12 hours and then distil the reaction mixture under vacuo on an electric water bath.

(3) Dissolve the remaining residue in water, filter and again evaporate to dryness on a water bath.

(4) To the dried residue add carefully 6–12 ml dry solvent ether, filter, evaporate the solvent and then dry the product in an oven maintained at 100°C.

The yield of the crude product is 5.6 g having mp 162–164°C.

5. Precautions

(1) The hydrolysis of ethylpropane-1, 1, 2, 3-tetracarboxylate in the presence of dilute HCl should be carried out by gentle refluxing for not less than 12 hours to get a better yield of tricarballylic acid.

(2) The crude product is easily recovered by removing the aqueous phase by distillation and taking up the residue with solvent ether.

6. Recrystallization. The crude product may be recrystallized either from water or ether. The yield of the pure product is 5.4 g having mp 165–166°C.

7. Theoretical yield/Practical yield. The theoretical yield is calculated from the equation under theory (Setp-III, 2) as given below :

332 g of Ethylpropane-1, 1, 2, 3-tetracarboxylate upon hydrolysis gives :

Tricarballylic Acid = 176.13 g

$\therefore$ 11 g of Ethylpropane-1, 1, 2, 3-tetracarboxylate shall yield

$$\text{Tricarballylic Acid} = \frac{176.13}{332} \times 11 = 5.84 \text{ g}$$

Hence, Theoretical yield of Tricarballylic Acid = **5.84 g**

Reported Practical yield = 5.6 g

$$\text{Therefore, Percentage Practical yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

$$= \frac{5.6}{5.84} \times 100 = \mathbf{95.89}$$

8. Physical Parameters. Tricarballylic acid is usually obtained as large orthorhombic prisms from water or ether having mp 166°C. It has three dissociation constant values, namely : K_1 at 30°C = 3.25×10^{-4} ; $K_2 = 2.65 \times 10^{-5}$; $K_3 = 1.48 \times 10^{-6}$. It is found that at 18°C, 50 g dissolve in 100 ml water and 0.9 g dissolve in 100 ml ether ; very soluble in ethanol. The trisodium salt is, however, neutral to litmus.

9. Uses. There is evidence that proteins not connected with blood coagulation usually contain β-carboxyglutaric acid so that the carboxylation phenomenon could be distributed widely.

10. Questions for *Viva-Voce*

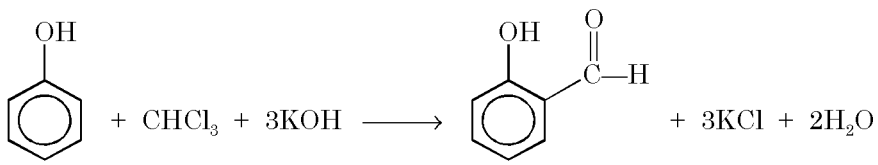
(1) What is the basis of reactions involved in the synthesis of Tricarballylic Acid ?

(2) Is it necessary in a multistep synthesis to purify the products at each step ? Explain.

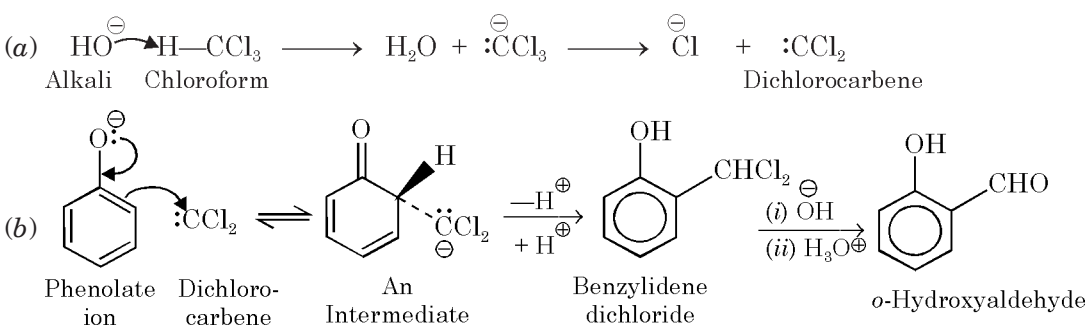
(3) What are the necessary precautions to be taken while handling a deadly poisonous chemical like Potassium Cyanide (KCN) in a laboratory ?

4.7.10 REIMER-TIEMANN REACTION

The formation of *phenolic aldehydes* from phenols, chloroform and alkali is known as the **Reimer-Tiemann Reaction*,** as shown under :



This particular overall *formylation reaction* is of ample interest because of the following critical steps involved in the course of Reimer-Tiemann Reaction as illustrated below :



In Equation (*a*), chloroform and alkali interacts to give rise to the formation of the reactive intermediate, dichlorocarbene.

In Equation (*b*), the resulting dichlorocarbene and the phenolate ion undergoes a reversible reaction to form an intermediate, which subsequently loses a proton and then gains a proton to yield the benzylidene dichloride. The benzylidene dichloride on being subjected to a treatment with an alkali followed by the hydronium ion yields the corresponding *ortho*-hydroxy aldehyde (or salicylaldehyde).

Evidently, in the case of **'phenol'** the main product is salicylaldehyde ; however, to a certain extent the *para*-isomer is also formed.

Thus, the *two* isomers (*i.e., ortho*-and *para*-) may be separated by subjecting the mixture to steam distillation, whereby only the *ortho*-isomer is steam volatile by virtue of the fact

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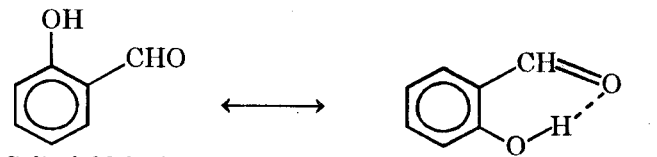
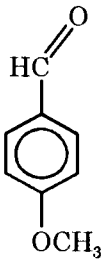
* Reimer, K., and F. Tiemann., *Ber.* **9,** 824, 1268, 1285 (1876) ; Wynberg, H., *Comp. Org. Syn* **. 2.** 769-775 (1991).



Salicylaldehyde ⟷ Intramolecular H-bonding (Salicylaldehyde)

4.7.10.1 *para*-Anisaldehyde

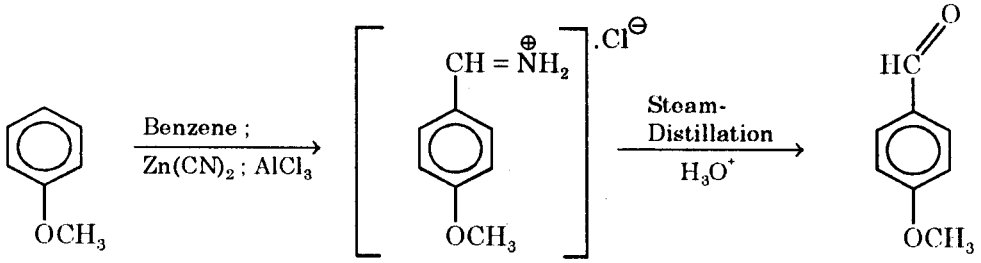
4.7.10.1.1 Chemical Structure



p-Anisaldehyde

4.7.10.1.2 Synonyms. 4-Methoxybenzaldehyde ; Anisic aldehyde.

4.7.10.1.3 Theory



Anisole (108.14) — An Imine hydrochloride — *p*-Anisaldehyde (136.15)

The anisole in the presence of zinc cyanide and dry $AlCl_3$ gives rise to the formation of an imine hydrochloride, which upon steam distillation yields the desired product *p*-Anisaldehyde.

4.7.10.1.4 Chemicals Required. Anisole (pure) : 30 g ; Sodium-dried Benzene : 75 ml ; Zinc cyanide (POISON) : 52 g ; Anhydrous Aluminium Chloride : 45 g ; Dilute Hydrochloric Acid (6 N) : q.s. ; Anhydrous Magnesium sulphate : 10 g.

4.7.10.1.5 Procedure. The various steps involved are as follows :

(1) Transfer 30 g (30 ml, 0.28 mol) anisole, 75 ml sodium-dried benzene (**Caution**) ; and 52 g (0.44 mol) of powdered zinc cyanide in the previously equipped 500 ml three-necked reaction flask.*

* A 500 ml 3-necked round bottom flask is equipped with a reflux condenser (preferably double-surface), an efficient Hg-sealed variable-speed mechanical stirrer and a wide inlet tube (to avoid possible clogging by the solid precipitate) extending almost to the bottom of the vessel.

(2) Chill the reaction mixture in a cold water bath, start the stirrer gently, and introduce a rapid and steady inlet of dry HCl-gas for 60 minutes, as described under the synthesis of **Flopropione** (section 4.7.6.1).

(3) Disconnect the gas-inlet tubing, and without stopping the mechanical stirrer, introduce carefully 45 g of finely powdered anhydrous aluminium chloride in small lots at intervals.

(4) Immediately replace the gas-inlet tubing and continue passing in a slow stream of HCl-gas while maintaining the mixture at 40–50°C on an electric water-bath for 3–4 hours.

(5) Allow the reaction mixture to cool somewhat and then quickly pour the reaction mixture with constant stirring into an excess of dilute HCl (6 N) ; when the resulting imine hydrochloride gets separated as a heavy precipitate.

(6) The resulting reaction mixture is refluxed for about 30 minutes so as to decompose the *imine hydrochloride* formed and subject it to steam-distillation.

(7) Separate the organic layer in the distillate by means of a separating funnel, dry with a small amount of anhydrous magnesium sulphate and distil off the benzene.

(8) Continue the distillation by making use of an air-bath and collect the anisaldehyde as a fraction having a bp ranging between 245.5–247.5°C with a yield of 34.2 g.

The crude product may be further purified by subjecting it to distillation once again but under vacuo, bp 134–135°C/12 mm Hg.

4.7.10.1.6 Precautions

(1) The reagents must be perfectly dry in this synthesis.

(2) HCl-gas generated should also be dried adequately before passing into the reaction-mixture.

(3) The intermediate product, imine hydrochloride, must be first separated by adding dilute HCl, and subsequently decomposed as far as possible by refluxing the reaction mixture.

(4) The benzene must be separated first-by distillation before proceeding to the actual recovery of the desired product by further distillation at an elevated temperature.

4.7.10.1.7 Theoretical yield/Practical yield. The theoretical yield is calculated from the equation under theory (section 4.7.10.1.3) as given under :

108.14 g of Anisole on interaction with requisite reagents

yield *p*-Anisaldehyde = 136.15 g

$\therefore$ 30 g of Anisole shall yield *p*-Anisaldehyde $= \frac{136.15}{108.14} \times 30 = 37.70$ g

Hence, Theoretical yield of *p*-Anisaldehyde = **37.70 g**

Reported Practical yield = 34.2g

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{34.2}{37.7} \times 100 = \mathbf{90.72}$

4.7.10.1.8 Physical Parameters. *p*-Anisaldehyde is obtained as an oily liquid, bp 248°C ; mp 0°C ; d_4^{15} 1.119 ; n_D^{13} 1.5764. It is found to volatile in steam. It is very slightly soluble in water ; and quite miscible with alcohol and ether.

4.7.10.1.9 Uses

(1) It possesses fungistatic activity

(2) It is employed as a carminative agent.

(3) It is also used as a flavouring agent.

(4) It is used in perfumery and toilet soaps.

4.7.10.1.10 Questions for *Viva-Voice*

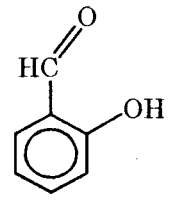
(1) How would you separate the *ortho-* and *para*-isomers of salicylaldehyde ? Explain.

(2) How do we accomplish the decomposition of the *'imine hydrochloride'* formed in the synthesis of *p*-anisaldehyde.

(3) Why is it always recommended to distillate a liquid organic compound under reduced pressure (*i.e.,* under vacuo) ? Explain.

4.7.10.2 Salicylaldehyde

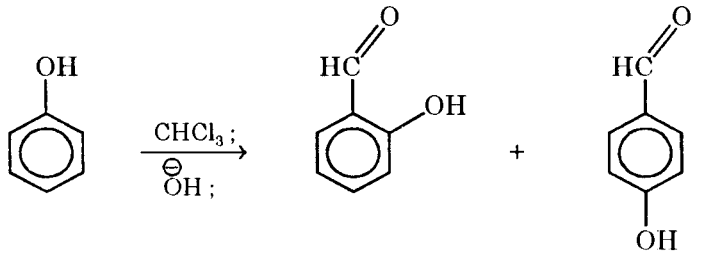
4.7.10.2.1 Chemical Structure



Salicylaldehyde

4.7.10.2.2 Synonyms. 2-Hydroxybenzaldehyde ; Salicylic aldehyde.

4.7.10.2.3 Theory



Phenol (94.11) | *o*-Salicylaldehyde **[Steam volatile]** | *p*-Salicylaldehyde **[Not steam-volatile]**

Phenol reacts with chloroform in an alkaline medium (OH^-) to give rise to the formation of *ortho-* and *para*-isomers of salicylaldehyde. The mechanism of the above reaction has already been explained earlier (under Reimer-Tiemann reaction ; section 4.7 J). Obviously, a mixture of both *ortho-* and *para*-isomers are formed simultaneously in the products of reaction ; however,

the desired former isomer may be separated conveniently by steam-distillation, while the later remains behind in the reaction flask.

4.7.10.2.4 Chemicals Required. Sodium Hydroxide (Pellets) : 60 g ; Phenol : 18.8 g ; Chloroform : 45 g ; Dilute Sulphuric Acid (6 N) : q.s. ; Solvent Ether : q.s. ; Sodium Metabisulphite : 25 g ; Anhydrous Magnesium Sulphate : q.s.

4.7.10.2.5 Procedure. The steps to be adopted in this synthesis are enumerated below :

(1) Transfer a moderately warm solution of 60 g of NaOH in 60 ml water in the 1 L 3-necked reaction flask*, add to it a solution of 18.8 g (0.266 mol) of phenol (Caution)** in 20 ml of water and stir gently.

(2) Maintain the temperature of the reaction mixture in the flask meticulouly between 60–65°C by heating on a thermostatically controlled electric water-bath ; **while taking every possible care not to allow the crystalline sodium phenoxide to separate out.**

(3) Add 45 g (30.1 ml ; 0.5 mol) of chloroform in three separate lots at an interval of 15 minutes down the condenser right into the reaction flask.

Note : *It is necessary to maintain the temperature of the well-stirred reaction mixture preferably between 65–70°C during the addition of chloroform which may be accomplished by immersing the flask in a thermostatically controlled electric water bath.*

(4) Finally, the contents of the flask is heated on a boiling water bath for 60 minutes to allow the reaction to complete.

(5) Distil off the excess of chloroform from the alkaline solution by means of steam-distillation.

(6) Allow the resulting orange coloured solution to attain room temperature, acidify carefully with dilute sulphuric acid. Again steamdistil the practically colourless liquid unless and until no more oily droplets are given out.

(7) The residue in the flask is set aside for the isolation of **Salicylaldehyde.**

The residue obtained above is filtered while hot through a fluted filter paper so as to get rid of the resinous matter ; and extract the cold filtrate with three successive quantities of ether (each of 25 ml). Distil off the ether, and the yellow solid thus obtained is eventually recrystallized from hot water to which a few ml of sulphurous acid (H_2SO_3) has been added. The yield of the *para*-hydroxybenzaldehyde, obtained as colourless crystals, is 1.5–2.2 g, having mp ranging between 115–116°C.

(8) The distillate obtained in step (6) is extracted immediately with solvent ether, at least twice 40 ml each time, a major portion of ether removed from the extract by distillation over a preheated water bath with the help of a *rotary thin film evaporator.*

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* A neat and clean 1L three-necked round bottom ftask is duly filted with a double-surface reflux condenser, a thermostatically controlled mechanical stirrer, and a thermometer, the bulb of which should be within 2 cm of the bottom of the flask.

** **Caution.** Pure phenol is very caustic in nature, therefore, it should be handled carefully with surgical gloves on.

(9) Quickly, transfer the resulting residue, to a small glass-stoppered flask, add almost twice its volume with a saturated solution of *sodium metabisulphite,* and shake the contents thoroughly and vigorously for 30 minutes preferably with a mechanical stirrer ; and keep it aside for 60 minutes.

(10) The resulting paste of **'bisulphite compound'** thus obtained is filtered in Büchner funnel under suction, wash with a little spray of ethanol ; and ultimately with a little spray with solvent ether to get rid of **phenol** completely.

(11) The **'bisulphite compound'** is now decomposed by warming gently in a 100 ml round bottomed flask, containing dilute sulphuric acid, on a water bath ; cool the decomposed product to ambient temperature, and extract the salicyl aldehyde with ether and dry the ethereal extract by adding anhydrous $MgSO_4$.

(12) The solvent ether is removed completely by **flash distillation*** ; and finally distil the residue thereby collecting the desired product, salicylaldehyde, as a colourless liquid between 195–197°C, with a yield of 8.95 g.

4.7.10.2.6 Precautions

(1) Special care has to be taken so that crystalline sodium phenoxide is NOT knocked out of the reaction mixture.

(2) The addition of chloroform should be in small lots (preferably three) within a gap of at least 15 minutes.

(3) After distilling off the excess amount of chloroform by steam distillation, allow the orange-coloured solution to attain room temperature and then acidify carefully with dilute H_2SO_4 till it becomes colourless.

(4) The **'bisulphite compound'** has to be decomposed by means of dilute H_2SO_4.

4.7.10.2.7 Theoretical yield/Practical yield. The theoretical yeild is calculated from the equation under theory (section 4.7.10.2.3) as given below :

94.11 g of Phenol on reaction with chloroform in an alkaline medium shall yield Salicylaldehyde = 122.12 g

$\therefore$ 18.8 g of Phenol shall yield Salicylaldehyde $= \frac{122.12}{94.11} \times 18.8 = 24.4$ g

Hence, theoretical yield of Salicylaldehyde = **24.4 g**

Reported Practical yield = 8.95 g

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{8.95}{24.4} \times 100 = \mathbf{36.68}$

4.7.10.2.8 Physical Parameters. Salicylaldehyde is obtained as a clear and colourless oily liquid, having a bitter-almond like distinct odour, and a burning taste. Its physical characteristics are : bp 196–197°C ; mp –7°C ; d_4^{20} 1.167 ; n_d^{20} 1.5735. It is found to be slightly

* **Flash Distillation.** It is a device to carry out distillation of small volumes, using a Claisen flask fitted with a fractionating side-arm.

soluble in water ; and fairly soluble in ether and ethanol. It gives a characteristic and distinct orange colouration with sulphuric acid.

4.7.10.2.9 Uses

(1) It is invariably used in perfumery.

(2) Catechol is prepared from salicylaldehyde which is used as an antiseptic agent.

4.7.10.2.10 Questions for *Viva-Voce*

(1) How would you prevent the separation of crystalline sodium phenoxide in this preparation ?

(2) Why is it required to add the requisite quantity of chloroform into the reaction mixture in 3 lots at an interval of 15 minutes at a temperature maintained between 60–65°C ?

(3) How do we get the 'bisulphite compound' ?

(4) How would you accomplish the decomposition of the 'bisulphite compound' ?

(5) What do you understand by 'Flash Distillation' ?

4.8 SELECTED MEDICINAL COMPOUNDS

A good, solid, and basic fundamental knowledge of organic, inorganic and physical chemistry is an absolute necessity in the wonderful and amazing field of **'medicinal chemistry'.** In reality, it embraces several wide areas of meaningful scientific research spanned from the **"most applied"** in one end to the **"most academic"** to the other end.

The *'search'* for a **' new drug molecule'** is an everlasting phenomenon that utilizes the utmost skill, wisdom and expertise of a wide spectrum of scientists *viz*., medicinal chemists, biotechnologists, pharmacologists, genetic engineers, material scientists, polymer scientists, organic chemists not only confined to Universities but also in the Research and Development Laboratories in pharmaceutical and allied industries.

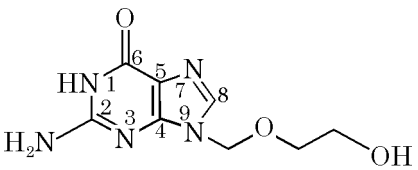
In this particular section an attempt has been made to select a few such medicinal compounds which have been used world-wide as a medicine for the control, management and cure of dreadful diseases of human beings.

The teachers intimately involved in conducting the **Practical Courses in Medicinal Chemistry** in various Universities, Institutions and Colleges offering Bachelor of Pharmacy (B. Pharm.,) and Master of Pharmacy (M. Pharm.,) Degrees throughout India and other developing countries shall find the treatment of the subject matter very convenient, educative and informative.

The Degree and Graduate students in Pharmacy Schools will also derive an impetus to creative thinking of actually synthesizing a good number of **'medicinal compounds'**, used frequently as potent drugs, in a reasonably good *'pharmaceutical chemistry laboratory'* thereby enhancing their knowledge and having a good grasp of the intricacies involved in preparing them.

4.8.1 Acyclovir

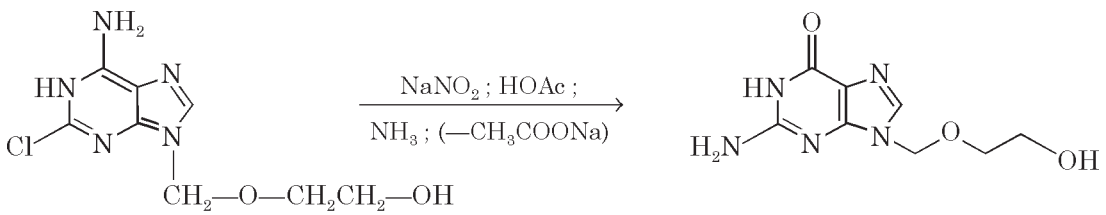
4.8.1.1 Chemical Structure



Acyclovir

4.8.1.2 Synonyms. Acycloguanosine* ; 2-Amino-1, 9-dihydro-9-[(2-hydroxyethoxy) methyl]-6H-purin-6-one ; Cargosil ; Zovirax.

4.8.1.3 Theory



2-Chloro-9-(2-Hydroxy-ethoxymethyl) adenine (205.71)

Acyclovir (225.21)

The substituted adenine *i.e.,* 2-chloro-9-(2-hydroxyethoxy-methyl) adenine is treated with pure sodium nitrite in glacial acetic acid and ammonia gas is passed through the reaction mixture for a stipulated period when the amino function gets rearranged from C-6 to C-2 together with a carbonyl moiety at C-6. Besides, there is a shift of double bond between positions from 2-3 and 5-6 to 2-3 and 4-5.

4.8.1.4 Chemicals Required. Sodium nitrite : 4.85 g ; 2-Chloro-9-(2-hydroxyethoxymethyl) adenine : 2.5 g ; Glacial Acetic Acid : 50 ml ; Ammonia gas : q.s. ; Ethanol : q.s. ;

4.8.1.5 Procedure. The steps followed are as follows :

(1) Solid sodium nitrite (4.85 g) was added at an ambient temperature (RT**) with constant stirring over a span of 60 minutes, in small lots at intervals, into a solution of 2.5 g of 2-chloro-9-(2-hydroxyethoxymethyl) adenine in 50 ml of glacial aceitic acid in a 250 ml round bottomed flask fitted with a mechanical stirrer, an inlet for NH_3-gas and an air-condenser fitted with a $CaCl_2$-guard tube.

(2) The reaction mixture was stirred for an additional 4 hours and 30 minutes in an atmosphere of ammonia gas.

(3) The resulting white precipitate was removed by filtration in a Büchner funnel under suction, washed with a spray of cold acetic acid ; and then triturated nicely with cold water to get rid of the sodium acetate present.

(4) The white solid product was retained duly. The combined acetic acid filtrate and wash was carefully evaporated under reduced pressure at 40°C bath temperature, and the resulting residual oil triturated again with cold water.

---

*Schaeffer, H.J., U.S. Patent 4, 199, 574 ; April 22, 1980 ; assigned to Burroughs Wellcome.

**RT = Room Temperature.

(5) The resulting solid material was combined with the previously retained/isolated white solid and the combined solids dried and weighed.

The yield of the crude product was 1.30 g having mp 250-251°C.

4.8.1.6 Precautions

(1) The sodium nitrite must be added in small lots at intervals over a span of 60 minutes.

(2) The reaction mixture should be stirred constantly for almost 4 1/2 hours in an atmosphere of ammonia gas to facilitate the intramolecular changes.

(3) The crude product needs to be recrystallized either from ethanol methanol.

4.8.1.7 Recrystallization. The crude product is recrystallized from ethanol to obtain a pure product having mp 256.5-257°C and yield 1.25 g.

4.8.1.8 Theoretical Yield/Practical Yield. The theoretical, yield is calculated from the equation under theory (section 4.8.1.3.) as stated under :

205.71 g of 2-Chloro-9-(2-hydroxyethoxymethyl) adenine on reacting with

$NaNO_2/NH_3$/HOAC yields Acyclovir = 225.21 g

∴ 4.85 g of 2-Chloro-9-(2-hydroxyethoxymethyl) adenine

shall yield Acyclovir $= \frac{225.21}{205.71} \times 4.85 = 5.31$ g

Hence, Theoretical yield of Acylovir = **5.31 g**

Reported Practical yield = 1.30 g

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{1.30}{5.31} \times 100 =$ **24.48**

4.8.1.9 Physical Parameters. Acyclovir is obtained as colourless crystals from methanol mp 256-257°C.

4.8.1.10 Uses.

(1) It is invariably employed in the treatment and prophylaxis of infections due to *Herpes simplex** or *Varicellazoster* viruses.

(2) It is used broadly as an antiviral agent.

4.8.1.11 Questions for *Viva-Voce*

(1) How would you prepare an antiviral agent from 2-Chloro-9-(2-hydroxyethoxy methyl) adenine ?

(2) Is the conversion of the adenine derivative to acyclovir an intramolecular rearrangement ? Explain.

(3) How would you remove the water-soluble sodium acetate obtained as the by-product from the reaction mixture finally ?

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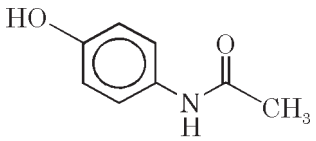
*An infections disease is characterized by thin-walled vesicles that tend to recur in the same area, at a site where the mucous membranes joins the skin.

4.8.2 Acetaminophen

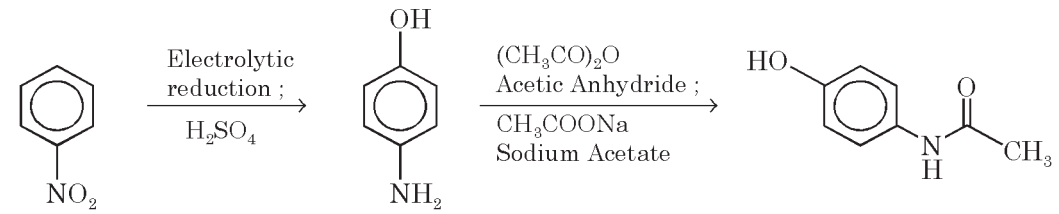
4.8.2.1 Chemical Structure



Acetaminophen

4.8.2.2 Synonyms. Paracetamol* ; N-(4-Hydroxyphenyl) acetamide ; *p*-Acetamidophenol ; *p*-Acetylaminophenol ; N-Acetyl-*p*-aminophenol ; Calpol ; Tylenol ; APAP.

4.8.2.3 Theory



Nitrobenzene (123.11) — *p*-Aminophenol (109.13) — Aectaminophen (151.17)

Nitrobenzene on being subjected to electrolytic reduction in the presence of sulphuric acid yields *para*-aminophenol which on treatment with acetic anhydride and sodium acetate gives rise to the production of acetaminophen (or paracetamol).

4.8.2.4 Chemicals Required. Nitrobenzene : 13 g (10.77 ml) ; Dilute H_2SO_4 (2N) : 25 ml ; Calcium Carbonate : q.s. ; Benzene : 100 ml ; Activated Carbon : 10 g ; Sodium hydrosulphite : 0.1 g ; Anhydrous sodium Acetate : 7.5 g ; Acetic Anhydride : 13.5 g.

4.8.2.5 Procedure. The various steps are adopted as follows :

(1) A reaction mixture consisting of 13 g (10.77 ml) nitrobenzene 100 ml water plus 25 ml of dilute H_2SO_4 (2N) was subjected to *'electrolytic reduction'* ; which yielded 11.5 g of *p*-aminophenol (checked by assaying *p*-aminophenol from the reaction mixture).

(2) The resulting reaction mixture containing *p*-aminophenol (11.5 g) is neutralized, while at a temperature ranging between 60-65°C, to a pH of 4.5, with pure calcium carbonate carefully.

(3) The precipitate of $CaSO_4$ thus obtained is filtered off, the precipitate is washed with hot water (65°C) and the filtrate and wash water then combined.

(4) The solution obtained above is subsequently extracted twice with 12.5 portions of benzene ; and the aqueous phase is treated with 0.5 part by weight, for each part of *p*-aminophenol present, of activated carbon (approx. 6 g) and the latter filtered off.

(5) The activated carbon is regenerated by treatment with hot dilute caustic followed by a hot dilute acid wash, and reused a minimum of *three times* (recycled).

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*Pearson *et. al. J. Am. Chem. Soc.,* **75**, 5907 (1953).

(6) To the filtrate thus obtained add about 0.1 g of sodium hydrosulphite (or sodium sulphite) and 7.5 g of anhydrous sodium acetate in about 13.5 g acetic anhydride at 40°C.

(7) The above reaction mixture is cooled between 8-10°C, stirred and maintained at this particular temperature for 60 minutes.

A crystalline pure product, paracetamol, 13.5 g having mp 169-170.5°C, is obtained.

4.8.2.6 Precautions

(1) The *electrolytic reduction* of nitrobenzene is to be carried out very carefully.

(2) The actual formation of *p*-aminophenol in the reaction mixture has to be assayed periodically to the maximum yield.

4.8.2.7 Recrystallization. The product may be recrystallized by dissolving in minimum quantity of hot water when a beautiful large monoclinic prisms obtained, 13 g, having mp 169.5 – 170.5°C.

4.8.2.8 Theoretical Yield/Practical Yield. The theoretical yield may be calculated from the equation under theory (section 4.8.2.3) as stated under :

123.11 g of Nitrobenzene after conversion to *o*-Aminophenol yields

Acetaminophen = 151.17 g

$\therefore$ 13 g of Nitrobenzene shall yield Acetaminophen $= \frac{151.17}{123.11} \times 13 = 15.96$ g

Hence, Theoretical yield of Acetaminophen = **15.96 g**

Reported Practical yield = 13.5 g

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{13.5}{15.96} \times 100 =$ **84.59**

4.8.2.9 Physical Parameters. Acetaminophen is obtained as large monoclinic prisms from water, mp 169-170.5°C ; d_4^{21} 1.293 ; uv_{max} (ethanol) : 250 nm ($\in$ 13800). It is found to be very slightly soluble in cold water, considerably more soluble in hot water ; soluble in ethanol, methanol, dimethylformamide (DMF), ethylene dichloride, acetone and ethyl acetate ; slightly soluble in solvent ether ; and almost insoluble in petroleum ether, benzene and pentane. It has a slightly bitter taste ; pH (Saturated solution) 5.3 to 6.5 ; and pKa 9.51.

4.8.2.10 Uses

(1) It is invariably used as an effective antipyretic and analgesic.

(2) It is also effective in the treatment of a wide variety of arthritic and rheumatic conditions involving musculoskeletal pain as well as the pain due to headache, *dysmenorrhea*, myalgias*** and *neuralgias****.

***Dysmenorrhea :** Pain caused in association with menstruation.

****Myalgias :** Tenderness or pain in the muscles ; muscular rheumatism.

*****Neuralgias :** Severe sharp pain occurring along the course of a nerve. It is caused by pressure built up on nerve trunks.

(3) It is broadly and safely recommended for the symptomatic management of pain and fever ; however, it has no antiinflammatory activity.

4.8.2.11 Questions for *Viva-Voce*

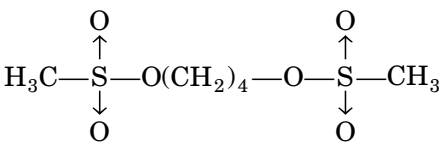
(1) How would you synthesise acetaminophen ?

(3) What do you understand by **'electrolytic reduction'** ? Explain.

(3) How does it act on the hypothalemic heat-regulating centre ? Explain.

4.8.3. Busulfan

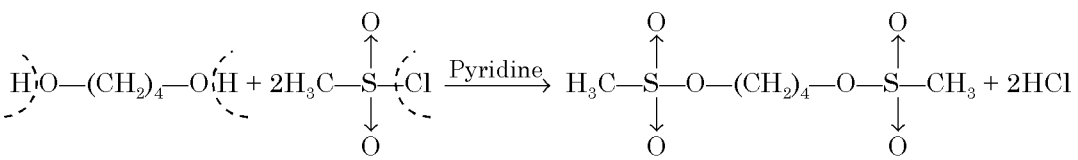
4.8.3.1 Chemical Structure



Busulfan

4.8.3.2 Synonyms. 1, 4-Butanediol dimethylsulphonate ; Busulphan ; 1, 4-di (Methanesulphonyloxy) butane ; Mitosan ; Sulfabutin ;

4.8.3.3 Theory



1, 4-Butanediol (90.12) | Methane sulphonyl chloride (114.55) | Busulfan (246.31)

One mole of 1, 4-Butanediol reacts with two moles of methane sulphonyl chloride in the presence of pyridine to yield one mole of busulfan and two moles of HCl are eliminated.

4.8.3.4 Chemicals Required. 1, 4-Butanediol (redistilled) : 3.6 g ; Pyridine (redistilled) : 10 ml ; Methane sulphonyl chloride (redistilled) : 9.6 g ; Acetone : 50 ml ; Ether : 50 ml.

4.8.3.5 Procedure. The various steps involved are as follows :

(1) 3.6 g (0.04 mol) of redistilled 1, 4-butanediol was dissolved in 10 ml of redistilled pyridine* and the resulting solution was chilled in an ice-bath.

(2) 9.6 g (0.08 mol) of redistilled methane sulphonyl chloride were added dropwise at such a regulated rate that the temperature was not permitted to go beyond 18 ± 2°C. After the completion of addition of methane sulphonyl chloride, the reaction mixture was allowed to stand at room temperature for a duration of 30 minutes, during which material time the temperature was elevated to ~ 60°C of its own (exothermic reaction).

(3) A thick precipitate of *pyridine hydrochloride* was formed.

*Pyridine being basic in nature gets oxidized with atmospheric oxygen thereby retarding its purity and reactivity ; hence, it should always be freshly redistilled before use in a reaction. The same holds good for **aniline.**

(4) The mass was cooled in ice-water and was treated with 30 ml of ice-cold water. A mere agitation with a glass rod shall yield a white crystalline solid.

(5) Filter of the white crystalline product in a Büchner funnel under vacuo, wash with a spray of iced water and allow to drain on the pump thoroughly.

The yield of the crude product was 7.75 g and had a mp 100°C.

4.8.3.6 Precautions

(1) Always make use of freshly redistilled 1, 4-Butanediol, Pyridine and Methane sulphonyl chloride in this reaction to obtain a pure product with better yield.

(2) The addition of methane sulphonyl chloride must be carried out **only dropwise** taking care that the temperature of the reaction mixture must not exceed 20°C, in any case.

(3) The pyridine hydrochloride is obtained as a thick precipitate, duly formed by the interaction of pyridine and HCl formed as a product of reaction. This has got to be removed and set apart.

4.8.3.7 Recrystallization. The crude product is recrystallized from a mixture of acetone and ether (1 : 1) to obtain beautiful small white needles with a yield of 7.50 g and mp 106-107°C.

4.8.3.8 Theoretical Yield/Practical Yield. The theoretical yield is calculated from the equation under theory (section 4.8.3.3) as stated under :

90.12 g of 1, 4-Butanediol on reacting with 114.55 g of Methane Sulphonyl chloride yields Busulfan = 246.31 g

$\therefore$ 3.6 g of 1, 4-Butanediol on reacting with 9.6 g of Methane Sulphonylchloride shall yield Busulfan $= \frac{246.31}{90.12} \times 3.6 = 9.84$ g

Hence, Theoretical yield of Busulfan = **9.84 g**

Reported Practical yield = 7.75 g

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{7.75}{9.84} \times 100 =$ **78.76**

4.8.3.9 Physical Parameters. It is obtained as crystals mp 114-118°C. It is found to be soluble in acetone at 25°C : 2.4 g/100 ml ; in ethanol : 0.1 g/100 ml ; almost insoluble in water, but will dissolve slowly as hydrolyses takes place.

4.8.3.10 Uses

(1) It is approved for the palliative treatment of chronic *granulocytic leukaemia**.

(2) It is also quite effective in the treatment of *polycythemia vera*** and *primary thrombocytocytosis*.***

---

*A polymorphonuclear leukocyte (*viz*, neutrophil, esosinophill, or basophil).

**A chronic, life-shortening mycloproliferative disorder of unknown etiology involving all bone marrow elements ; characterized by an increase in RBC mass and homoglobin concentration.

***Primary dissolution of thrombocytes (*i.e.,* platelet).

4.8.3.11. Questions for *Viva-Voce*

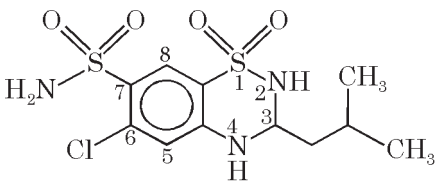
(1) Why is this reaction carried out in the presence of pyridine ?

(2) How does pyridine get eliminated from the reaction mixture ?

(3) Why do we add methane sulphonyl chloride only dropwise over a certain period and taking care that the temperature must not go beyond 20°C ?

4.8.4. Buthiazide

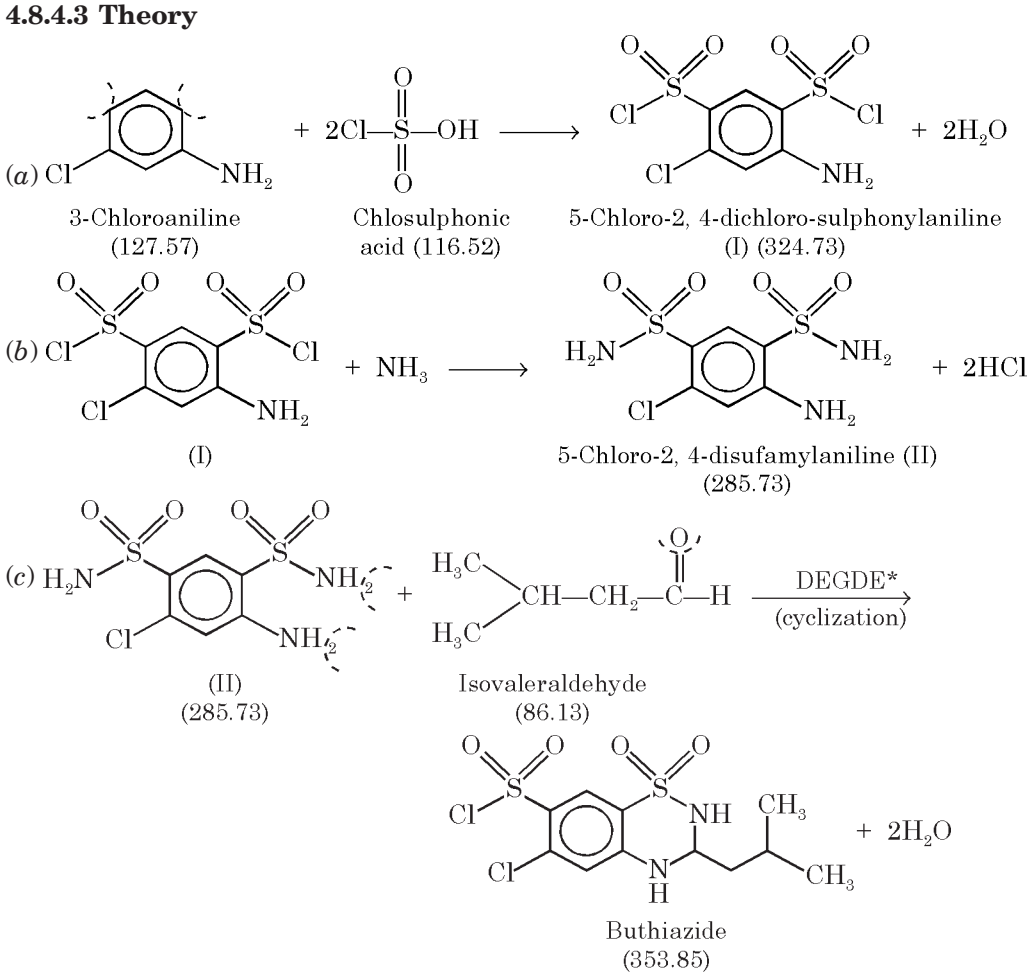
4.8.4.1 Chemical Structure



Buthiazide

4.8.4.2 Synonyms. 6-Chloro-3, 4-dihydro-3-isobutyl-7-sulphamoyl -1, 2, 4-benzothiadiazine-1, 1-dioxide ; Thiabutazide ; Butizide ; Isobutylhydrochlorothiazide.

4.8.4.3 Theory



(a) 3-Chloroaniline (127.57) + Chlosulphonic acid (116.52) → 5-Chloro-2, 4-dichloro-sulphonylaniline (I) (324.73) + $2H_2O$

(b) (I) + NH_3 → 5-Chloro-2, 4-disufamylaniline (II) (285.73) + 2HCl

(c) (II) (285.73) + Isovaleraldehyde (86.13) $\xrightarrow[\text{(cyclization)}]{\text{DEGDE*}}$ Buthiazide (353.85) + $2H_2O$

*DEGDE = Diethyleneglycol dimethylether.

The interaction of 3-chloroaniline and chlorosulphonic acid gives rise to the formation of an intermediate 5-chloro-2, 4-dichlorosulphonylaniline (I)* with the elimination of two moles of water. Subsequent amination of (I) with ammonia forms the corresponding sulphamyl derivative as 5-chloro-2, 4-disulfamylaniline (II) plus two moles of HCl. The resulting sulfamyl compound (II) is reacted with isovaleraldehyde in the presence of diethyleneglycoldimethyl ether, thereby undergoes cyclization, to yield buthiazide and two moles of water get eliminated.

4.8.4.4 Chemicals Required. 3-Chloroaniline : 19 g ; Chlorosulphonic acid (good-grade) : 32.2 ml ; Concentrated Ammonia (*d* 0.88) : 75 ml ; Dilute sulphuric acid (6N) : q.s. ; Diethyleneglycol-dimethylether : 15 ml ; Isovaleraldehyde : 6 g ; Saturated solution of HCl in Ethyl Acetate : 5 ml ; Dimethylformamide : 25 ml ; Ethanol : 100 ml.

4.8.4.5 Procedure. The synthesis may be accomplished in **three** following steps, namely.

Step-I. Preparation of 5-Chloro-2, 4-dichlorosulphonyl aniline (I) :

(1) Equip a 500 ml two-necked flask with a dropping funnel and a reflux condenser ; and attach the top-end of the latter to a device for the absorption of hydrogen chloride. Transfer 19 g (0.15 mol) of dry 3-chloroaniline in the reaction flask and 32.2 ml (58 g, 0.75 mol) of a good grade of chloro-sulphonic acid (**CAUTION :** *Highly corrosive chemical*) in the dropping funnel and provide a calcium-chloride guard-tube into the latter.

(2) Add the chlorosulphonic acid in small lots at intervals and shake the flask intermittently to ensure thorough mixing. When the addition has been completed, heat the reaction mixture on a water bath for at least 60-70 minutes so as to complete the reaction.

(3) Cool the resulting reaction mixture to ambient temperature and pour the oily mixture in a thin-stream with constant stirring with a glass rod into 300 g of crushed ice contained in a 1 L beaker.

[**Note :** *Carry out this operation very cautiously and carefully in an efficient fume cupboard since the excess of chlorosulphonic acid reacts vigorously with water.*]

(4) Rinse the flask with a small quantity of ice-water and add the rinsings to the contents of the beaker. Break up any lumps of solid material and stir the mixture for several minutes in order to obtain an even suspension of the granular white solid.

(5) Filter of the 5-chloro -2, 4-dichlorosulphonyl aniline (I) at the pump, and wash it with a little cold water ; press and drain well. **Use the crude product immediately in Step-II.**

Step-II. Preparation of 5-Chloro-2, 4-disulfamylaniline (II)

(1) Transfer the crude product (I) directly into the rinsed reaction flask, and add to it a mixture of 75 ml of concentrated ammonia solution (*d* 0.88) and 75 ml of DW. Mix the contents of the flask thoroughly, and heat the mixture with occasional swirling (*preferably in a fume cupboard*) to just below the boiling point for approximately 15-20 minutes. Product (I) shall be converted into a pasty suspension of the corresponding sulphonamide (II).

---

*The amino function in 3-chloroaniline directs the incoming sulphonylchloride function to the *ortho*- and *para*-position to yield (I).

(2) Cool the resulting suspension in ice, and then add dilute H_2SO_4 carefully with stirring until the mixture is just acidic to *Congo Red Paper*.

(3) Collect the product (II) on a Büchner funnel, wash with a little cold water and drain as completely as possible.

The yield of the crude product (II) is about 28 g, which is sufficiently pure for the next and the final Step-III.

Step-III. Preparation of Buthiazide

(1) 20 g of 5-Chloro-2, 4-disulphamylaniline (II) in 15 ml of diethyleneglycol dimethyl ether with 6 g of isovaleraldehyde are reacted in the presence of 5 ml of saturated solution of HCl in ethyl acetate between 80-90°C for a duration of about 60 minutes.

(2) The resulting reaction mixture is subjected to concentration under reduced pressure when an oily product precipitates on the addition of water.

(3) The precipitate is decanted off and sufficient ethanol added to the remaining oil when buthiazide crystallizes.

The yield of the crude buthiazide is about 16 g having mp ranging between 240.5-244°C.

4.8.4.6 Precautions

(1) In step-I, the addition of chlorosulphonic acid to 3-chloroaniline must be added in small lots at intervals with frequent stirring.

(2) In step-II, once the amination is complete, the reaction mixture must be acidified with dilute H_2SO_4 carefully to Congo Red Paper.

(3) In step-III, the reaction between compound (II) and isovaleraldehyde *i.e.,* the cyclization, to yield buthiazide is accomplished duly in the presence of DEGDE only.

4.8.4.7 Recrystallization. The crude buthiazide is recrystallized by dissolving in a minimum amount of dimethylformamide (DMF) and water. The pure product is obtained having mp 241 – 245°C with an yield of 14.5 g.

4.8.4.8 Theoretical Yield/Practical Yield. The theoretical yield is calculated from the Equation (*c*) under theory (section 4.8.4.3) as given below :

285.73 g of 5-Chloro-2, 4-disulfamylaniline on reacting with 86.13 g of Isovaleraldehyde yields Buthiazide = 353.85 g

$\therefore$ 20g of 5-Chloro-2, 4-disulphamylaniline shall yield

Buthiazide $= \dfrac{353.85}{285.73} \times 20 = 24.79$ g

Hence, the Theoretical yield of Buthiazide = **24.79 g**

Reported Practical yield = 16 g

Therefore, Percentage Practical yield $= \dfrac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \dfrac{16}{24.79} \times 100 =$ **64.5**

4.8.4.9 Physical Parameters. Buthiazide is obtained as crystals having mp 241-245°C [Werner *et. al. J. Am. Chem. Soc.,* **82,** 1161 (1960)] ; and from methanol + Chloroform having mp 228°C [Topliss *et. al. J. Org. Chem.* **26,** 3842 (1961)].

4.8.4.10 Uses

(1) It is used as a potent diuretic.

(2) It is invariably employed for oedema including the one associated with heart failure and for hypertension.

4.8.4.11 Question for *Viva-Voce*

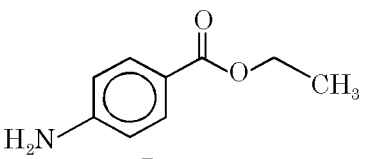
(1) What are '*thiazides*' (or '*benzothiadizines*') and their therapeutic value in medicinal chemistry ?

(2) Can you give the names of any *three* potent '*thiazide*' diuretics ?

(3) How would you explain the synthesis of 'Buthiazide' *vis-a-vis* the formation of the '*thiazide*' nucleus ?

4.8.5 Benzocaine

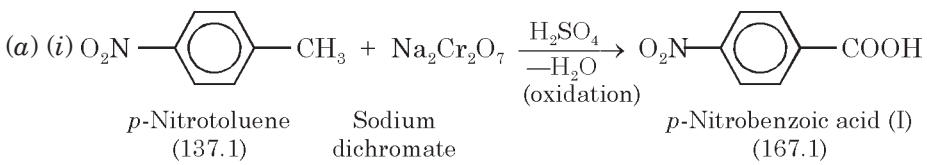
4.8.5.1 Chemical Structure



Benzocaine

4.8.5.2 Synonyms. 4-Aminobenzoic acid ethyl ester ; Ethyl *p*-amino-benzoate ; Americaine ; Anesthesin ; Orthesin ; Parathesin.

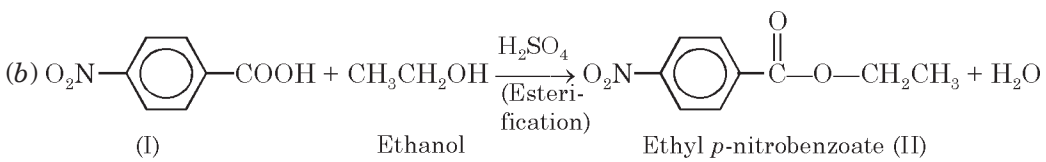
4.8.5.3 Theory



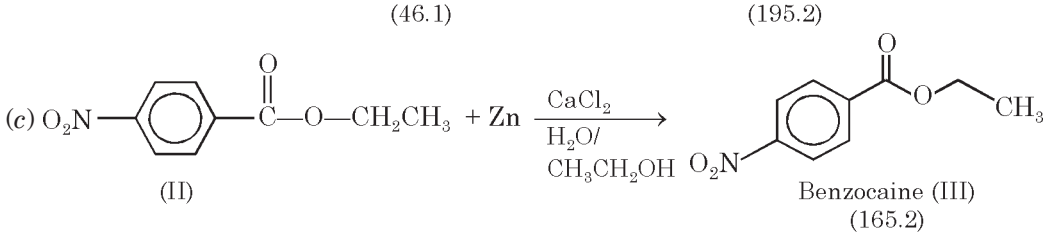
p-Nitrotoluene (137.1) — Sodium dichromate — *p*-Nitrobenzoic acid (I) (167.1)

$$(ii)\ Na_2Cr_2O_7 + 4H_2SO_4 \longrightarrow Na_2SO_4 + Cr_2(SO_4)_3 + 4H_2O + 3(O)\uparrow$$

Nescent Oxygen



(I) — Ethanol (46.1) — Ethyl *p*-nitrobenzoate (II) (195.2)



(II) — Benzocaine (III) (165.2)

The synthesis of *Benzocaine* starting from *p*-nitrotoluene is usually accomplished by means of **three** sequential reactions *i.e.,* Eq. (*a*) through Eq. (*c*) as given above.

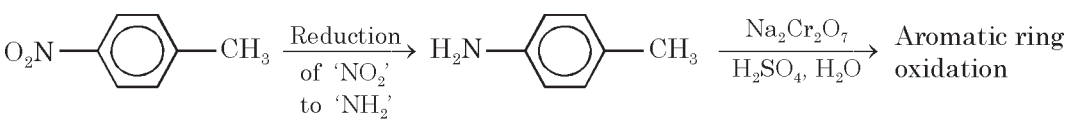
Eq. (*a*) shows the *oxidation* of *p-nitrotoluene* by sodium dichromate in an acidic medium (with H_2SO_4) to yield *p*-nitro benzoic acid (I) whereby the *methyl* function in the starting material gets oxidized to the corresponding *carboxylic* moiety due to the evolution of 3-moles of *nescent oxygen* as given in Eq. (*a*) (*ii*).

Eq. (*b*) depicts the *esterification* of (I) with ethanol in the presence of sulphuric acid whereby the corresponding ester *i.e.,* ethyl-*p*-nitrobenzoate (II) is formed with the abstraction of one mole of water.

Eq. (*c*) illustrates the *reduction* of (II) in the presence of Zn, calcium chloride and dilute acetic acid, whereby the *nitro* group at the *para*-position gets reduced to *amino* function ; and the desired product *i.e.,* Benzocaine (III) is obtained.

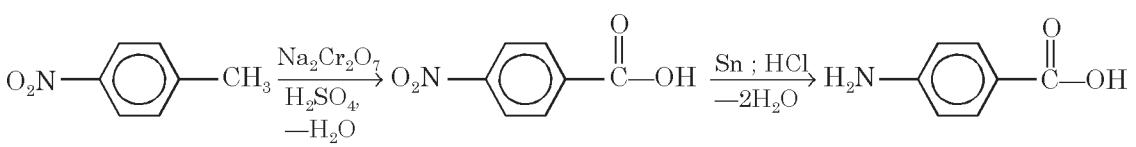
It is, however, pertinent to mention here that the aforesaid *three reactions,* namely : (*i*) **oxidation ;** (*ii*) **esterification** ; and (*iii*) **reduction** must be carried out in the **same sequence strictly,** otherwise one may not get the desired product.

Case-I : A situation where reduction of the *nitro* function precedes oxidation. In this particular instance an altogether new compound *para*-toluidine shall be formed which upon oxidation with sodium dichromate and sulphuric acid shall undergo **aromatic ring oxidation** instead, because '*anilines*' with strong oxidizing agents, *e.g.,* dichromate usually gives similar products.



p-Nitrotoluene *p*-Toluidine

Case-II. A similar situation wherein reduction of the *nitro* function precedes esterification. In this specific case the initial reaction involving the oxidation of *p*-nitrotoluene gives rise to the formation of *p*-nitrobenzoic acid which on further reduction with tin and HCl yields *p*-aminobenzoic acid (PABA) ; and PABA being soluble in both acid and base is rather *difficult to isolate.* Moreover, PABA may be isolated only under precisely *neutral conditions* and that too after removal of the metal ions which eventually form complexes with it.



p-Nitrotoluene *p*-Nitrobenzene acid *p*-Aminobenzoic acid [Difficult to Isolate]

Therefore, it is always advisible to employ the previously cited reaction sequence rigidly *viz*., oxidation-esterification-reduction, in order to circumvent these aforesaid difficulties. Further, the commercial production of benzocaine is usually carried out by **catalytic hydrogenation** in place of using **zinc dust**.

4.8.5.4 Chemicals Required

For Step-I. Sodium dichromate dihydrate : 20 g ; Conc. Sulphuric Acid (36 N) : 25 ml ; *p*-Nitrotoluene : 6.8 g ; NaOH [10% (w/v)] : 30 ml ; Decolourizing Carbon : 1.5 g ; Conc. Hydrochloric acid (12 N) : 20 ml.

For Step-II. *p*-Nitrobenzoic acid : 3.4 g ; Absolute Ethanol : 30 ml ; Conc. Sulphuric acid (36 N) : 5 ml ; NaOH [10% (w/v)] : 50 ml.

For Step-III. Calcium chloride : 1 g ; Ethanol (95%) : 55 ml ; Ethyl-*p*-nitobenzoate : 2.5 g ; Zine dust pure : 25 g ; Solvent Ether : 100 ml ; Sodium chloride : 100 g ; *n*-Pentane ; 50 ml.

4.8.5.5 Procedure. The synthesis of 'benzocaine' is accomplished in *three* different steps as given under :

Step-I. Oxidation of *p*-Nitrotoluene

(1) Dissolve 20 g (0.67 mol) of sodium dichromate dihydrate in 50 ml of water into a 250 ml round bottom flask. Slowly and carefully add 25 ml of concentrated sulphuric acid with frequent stirring into the above chromic acid solution (an exothermic reaction).

(2) Allow the reaction mixture to cool down to less than 50°C, and then add 6.8 g (0.05 mol) of *p*-nitrotoluene. Now add a few boiling chips (or stones) into the reaction flask, attach the Claisen head to the round bottom flask and place the thermometer adapter on the central connection of the Claisen head. Insert a thermometer (preferably 0-360°C) through the adapter right into the reaction solution and attach a double surface reflux condenser to the side connection of the Claisen head.

(3) Heat the reaction mixture gently to 75°C when an **exothermic reaction** could be seen by a sudden and rapid increase in the reaction temperature. Remove the source of heat for a while till the temperature starts falling and then replace the heat source once again. Reflux the contents for 60 minutes, allow it to cool for 15 minutes and pour it out 100 g of crushed ice in a 250 ml conical flask (*i.e.,* Erlenmeyer flask).

(4) Collect the solid precipitate in a Büchner funnel under suction, and wash the residue with two 30 ml portion of water.

(5) Transfer the solid residue into a 250 ml beaker, add 30 ml of water, and 30 ml of 10% aqueous NaOH solution to affect dissolution of *p*-nitrobenzoic acid. Warm the resulting mixture on a steam bath for 10 minutes to permit coagulation of residual chromium salts as their insoluble hydroxides and then filter by suction. Add 1.5 g of decolourizing carbon to the resulting filtered solution, heat the contents for 10 minutes ; and filter the mixture by gravity through a coarse filter paper.

(6) Prepare separately an aqueous acidic solution by adding 20 ml of concentrated HCl (12N) to 30 g of crushed ice in a 250 ml beaker. Now slowly and with constant stirring, pour the basic charcoal-decolourized solution (Step-5 above) into the aqueous acidic solution. At the end ensure that the pH of the resulting solution is strongly acidic (test with litmus paper).

(7) The resulting precipitate is filtered in a Büchner funnel under suction, wash the precipitate with 10 ml portions of water.

The yield of the crude *p*-nitobenzoic acid is 6.2 g having mp 240-241°C.

The crude product may be further recrystallized from ethanol to get 5.8 g of the pure product mp 241 – 242°C.

Step-II. Esterification of *p*-Nitrobenzoic Acid

(1) Transfer 30 ml of absolute ethanol to 3.4 g (0.02 mol) of *p*-nitrobenzoic acid in a 100 ml round bottom flask. Place a few anti-bumping chips into the flask, and attach a reflux condenser for heating under reflux.

(2) Add 5 ml of concentrated sulphuric acid to the reaction mixture through the condenser in small lots at intervals. Reflux the mixture for about 60 minutes until all the solid *p*-nitrobenzoic acid gets dissolved.

(3) Cool the reaction mixture to room temperature and pour the contents into a mixture of 50 ml of 10% aqueous NaOH solution and nearly 50 g of crushed ice.

(4) Filter the precipitate in Büchner funnel under suction and wash with a thin spray of cold water.

(5) The yield of the crude product is 2.95 g having mp ranging between 54.5-55°C.

The crude product may be recrystallized from a minimum volume of ethanol-water (1 : 1) to obtain 2.75 g of pure product mp 55-56°C.

Step-III. Reduction of Ethyl *p*-Nitrobenzoate.

(1) Transfer 1 g of calcium chloride in 12 ml of water placed in a 100 ml beaker ; and mix this solution with 55 ml of 95% (v/v) ethanol.

(2) Pour the resulting solution into a 250 ml round bottom flask that contains 2.5 g (0.013 mol) of ethyl *p*-nitrobenzoate (Step-II), add to it 25 g of Zn-dust, and attach to it a reflux condenser.

(3) Reflux the reaction mixture for 2 hours gently and at a stretch and then cool to room temperature.

(4) Separate the unreacted Zn-dust from the aqueous ethanolic solution in Büchner funnel under suction, and wash the filtered solid with two 25 ml portions of solvent ether.

(5) Extract the filtrate with 150 ml of water previously saturated with NaCl. Wash the aqueous layer twice with 25 ml portions of solvent ether. Combine all the ethereal layers together (including one obtained in (4) above ; and wash it with two successive portions each of 40 ml of water.

(6) Dry the resulting ethereal solution over anhydrous Mg SO_4, filter, and subsequently distil the ether on a steam bath to a final volume of 10 to 15 ml. Transfer the ethereal residue to an Erlenmeyer flask and add to it 20 ml of pentane to precipitate the desired product benzocaine.

The yield of the crude benzocaine is 1.58 g having mp 88-89.5°C.

4.8.5.6 Precautions

(1) The mild reduction of ethyl *p*-nitrobenzoate is required which is accomplished with Zn-dust and HCl obtained by the interaction of $CaCl_2$ and water.

(2) The ethereal layer needs to be dried as far as possible with anhydrous $MgSO_4$ before distilling off the excess of ether on a water-bath.

(3) *n*-Pentane should be used carefully to separate out the precipitate of benzocaine from the concentrated ethereal fraction.

4.8.5.7 Recrystallization. The crude product is recrystallized from a minimum quantity of a mixture of ether and pentane (1 : 1) and the yield of the pure product is 1.40 g mp 89-90°C.

4.8.5.8 Theoretical Yield/Practical Yield. The theoretical yield is calculated from the equation under theory (section 4.8.5.3) as given below :

195.2 g of Ethyl-*p*-nitrobenzoate on reduction yields Benzocaine = 165.2 g

$\therefore$ 2.5 g of Ethyl-*p*-nitrobenzoate shall yield Benzocaine $= \frac{165.2}{195.2} \times 2.5 = 2.11$ g

Hence, Theoretical yield of Benzocaine = **2.11 g**

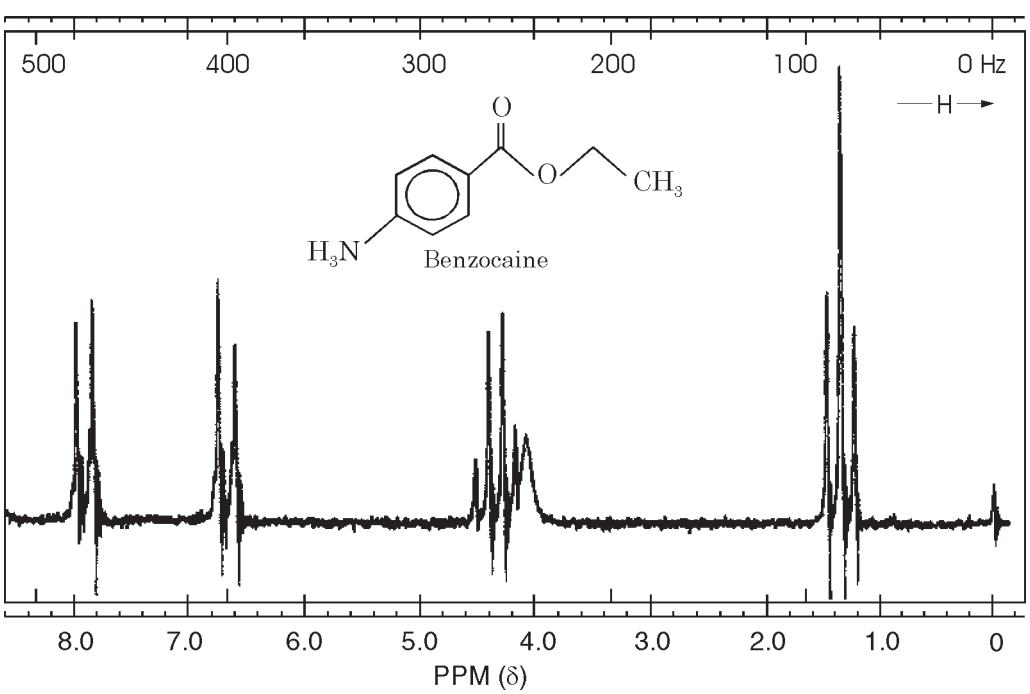
Reported Practical yield = 1.58 g

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{1.58}{2.11} \times 100 =$ **74.88**

4.8.5.9 Physical Parameters. It is obtained as rhombohedra crystals from ether, mp 88-90°C, and fairly stable in air .1 g Dissolves in about 2.5 L water, 5 ml ethanol, 2 ml $CHCl_3$, 4 ml ether, and in 30 to 50 ml of expressed *almond oil* or *olive oil*. It is also found to be soluble in dilute acids and its dissociation constant *p*K*a* is 2.5.

Following is the ^{1}H-NMR spectrum of benzocaine recorded in $CDCl_3$ solution.



4.8.5.10 Uses

(1) It is usually employed as an ointment to relieve pain associated with ulcers, wounds, burns, and mucous surfaces.

(2) It is also used as a lubricant and anaesthetic on intra-tracheal catheters, pharyngeal and nasal airways, nasogastric and endoscopic tubes etc.

(3) It is included in proprietory creams, lozenges, ointments, powders, sprays, and suppositories to relieve pain from damaged skin surfaces and inflamed mucous membranes.

(4) It is also used as on otic preparation for the temporary relief of ear pain.

4.8.5.11 Questions for *Viva-Voce*

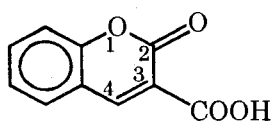
(1) What are the *three* sequential steps used in the synthesis of Benzocaine ?

(2) Can you give the names of *three* other esters used as 'local anaesthetics' ?

(3) What are the *six* different major uses of 'local anaesthetics' ? Explain

4.8.6. Coumarin-3-Carboxylic Acid

4.8.6.1 Chemical Structure



Coumarin-3-carboxylic acid

4.8.6.2 Synonyms. 2-Oxo-2H-1-benzopyran-3-carboxylic acid.

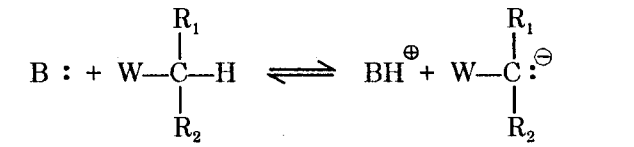
4.8.6.3 Theory. Coumarin-3-carboxylic acid is formed due to *condensation reactions*.

A *condensation reaction* is, therefore, caused due to the combination of two or more molecules to result into the formation of a *'new molecule'* with the elimination of a simple molecule, for instance : water. In general, the carbonyl compounds undergo condensation reactions initially by the process of *'addition'*, and then followed by *'elimination'*, usually carried out under basic conditions. In fact, the condensation reactions are specifically of immense utility for the ultimate construction (synthesis) of a *'complex compound'* starting from rather simpler organic compounds.

Condensation reactions with the carbonyl compounds essentially involve *nucleophilic addition*. It is, however, pertinent to mention here that since the *'active hydrogen component'* is not itself sufficiently nucleophilic to add to the carbonyl group, base removal of a proton from the α-position with respect to the active hydrogen component (*i.e.,* the most acidic position) is required.

Precisely the *'nucleophilic addition process'* may be regarded to accomplish in *three* important sequential steps, namely :

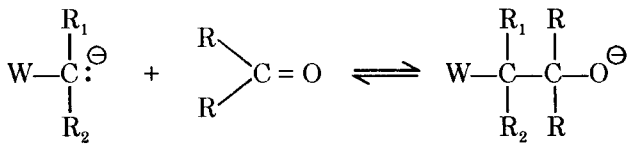
(*a*) *Acid-base Equilibrium Reaction between the Base and the Active-Hydrogen Component :*



Base | Active hydrogen component | Conjugate acid | Nucleophilic conjugate base

The base on interaction with an active hydrogen component undergoes a reversible reaction to yield a *conjugate acid* plus a *nucleophilic conjugate base.*

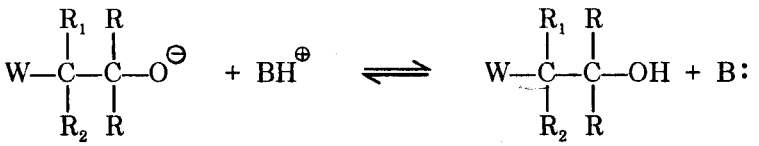
(*b*) *Nucleophilic Addition to the Carbonyl Compound*



Nucleophilic conjugate base | A carbonyl compound | Alkoxide addition product

The resulting nucleophilic conjugate base from Eq. (*a*) interacts with a carbonyl compound to give rise to the formation of an *'alkoxide addition product'*, a reversible reaction.

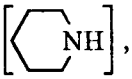
(*c*) *Protonation of the Alkoxide by the Conjugate Acid :*



Alkoxide addition product | Conjugate acid | An addition product

The alkoxide addition product obtained from Eq. (*b*) reacts with the conjugate acid obtained from Eq. (*a*) to yield an addition product together with the liberation of the free base [to be reutilized in Eq. (*a*)]*.

Importantly, the choice of the base catalyst normally used in a **carbonyl condensation reaction** is not only very critical but also extremely important. It has, however, been observed that the base chosen must be sufficiently basic in character and strength so as to enable the *removal of the* α*-hydrogen from the active hyrogen component* ; and *not* basic enough to cause *removal of the H-atom from the* α*-position of the carbonyl compound.* Therefore, it is an usual practice to select a **'base'** for condensation reactions so that the–'equilibrium concentration of the nucleophilic conjugate base of the active hydrogen component is reasonably low. In other words, the K*a* value for the conjugate acid of the base (BH^+) is 10^2 to 10^4 times greater than the K*a* of the active hydrogen component.

Example : Piperidine  , having *p*K*a* of $BH^+ = 11$, is invariably employed in condensation reactions in ease the active hydrogen component is diethyl malonate (*p*K*a* = 13).

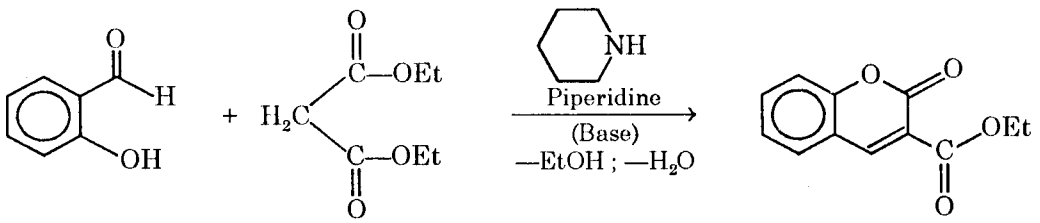
*The reactions from Eq. (*a*) through Eq. (*c*) are all reversible in nature.

The **synthesis** of Coumarin-3-carboxylic acid is often accomplished in **two** steps, namely :

(*i*) Preparation of 3-Carbethoxycoumarin, and

(*ii*) Preparation of Coumarin-3-carboxylic acid.

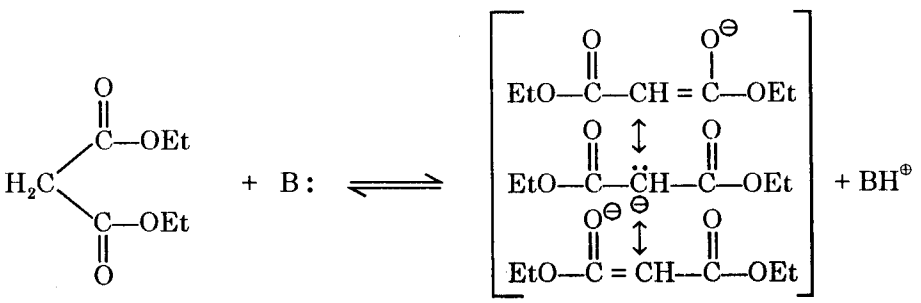
First Step. *Preparaton of 3-carbethoxy coumarin :*



Salicylaldehyde (122) | Diethyl malonate (160) | 3-Carbethoxycoumarin (218)

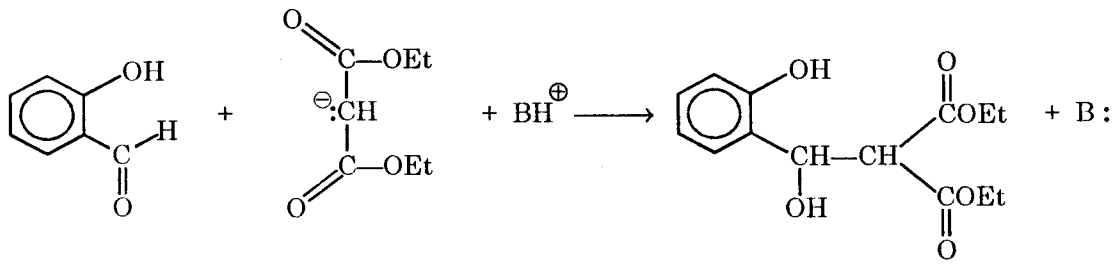
A mole each of salicylaldehyde and diethyl malonate undergoes condensation in the presence of a catalytic quantum of the base piperidine.

Mechanism. Diethyl malonate by reaction with the basic piperidine results into the formation of the **resonance stabilized diethyl malonate anion** as given below :



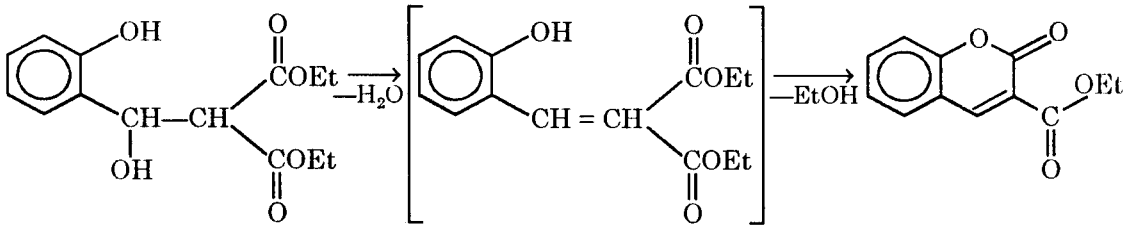
Diethyl malonate | Diethyl malonate anion

Consequently, the diethyl malonate anion adds on to the *carboxyl function* of salicylaldehyde, and then the *intermediate alkoxide* formed is duly protonated to yield the addition product as shown below :



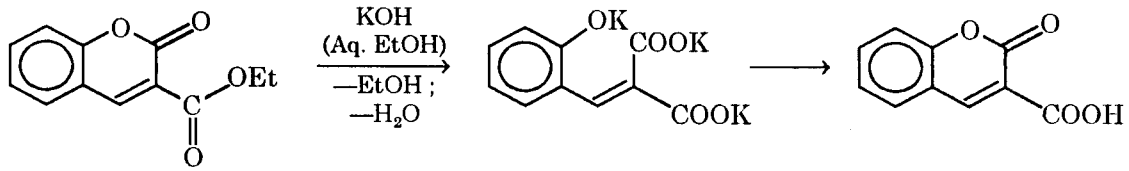
Salicylaldehyde | Diethyl malonate anion | Conjugate acid | An addition product [Intermediate] | Base

Subsequently, the *intermediate addition product* readily affords the loss of a mole of water and undergoes cyclization, by way of *transesterification**, to give rise to the final desired product *i.e.,* 3-carbethoxycoumarin as illustrated under :



[**Note.** *The cyclization reaction may either follow the elimination of water, as depicted above, or it may precede the elimination of water.*]

Second Step. *Preparation of Coumarin-3-carboxylic acid :*



3-Carbethoxy-coumarin (218)

Tri-potassium salt of *o*-hydroxy bonzylidene molonic acid

Coumarin-3-carboxylic acid (190.16)

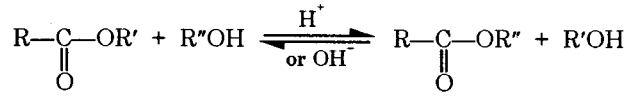
Coumarin-3-carboxylic acid is obtained by refluxing 3-carbethoxy coumarin with a solution of KOH in aqueous ethanol. Evidently, during the course of hydrolysis both the *ethyl ester* and the *cyclic ester* (*i.e.,* the lactone ring or the pyran ring) undergo rapid **cleavage** by the aforesaid *'base'* to form the corresponding tri-potassium salt of *ortho*-hydroxybenzylidenemalonic acid. Thus, acidification of this product affords instant hydrolysis whereby affecting reformation of the pyran ring (or lactone ring) thereby yielding the designated product coumarin-3-carboxylic acid.

4.8.6.4 Chemicals Required

For Step-I. Salicylaldehyde : 5 g ; Dieithyl malonate : 7.2 g ; Absolute Ethanol : 25 ml ; Piperidine (freshly distilled) : 0.5 ml ; glacial acetic acid : 0.02 ml ; Ethanol-water mixture (1 : 1) : 20 ml.

For Step-II. 3-Carbethoxy coumarin : 4 g ; Ethanol [95% (v/v)] : 25 ml ; Potassium hydroxide (pellets) : 4 g ; Dilute Hydrochloric acid (2N) [Prepared by dissolving 10 ml conc. HCl (12N) into 50 ml of DW] : 60 ml.

***Transesterification.** [*Alkoxy-de-alkoxylation* or *Alcoholysis of carboxylic esters*] : It is catalyzed by **acids** or **bases.** It is an equilibrium reaction and should be shifted in the desired direction.

Example : 

It has also been carried out with phase transfer catalysis, without an added solvent.

[March Jerry, Advanced Organic Chemistry, John Wiley & Sons (Asia) Pvt. Ltd., Singapore, 4th edn., 2001, p-397]

4.8.6.5 Procedure. The various steps involved in *Step-I* and *Step-II* are enumerated below in a sequential manner :

Step I : Preparation of 3-Carbethoxycoumarin :

(1) Transfer 5 g salicylaldehyde (0.041 mol), 7.2 g diethyl malonate (0.045 mol), 25 ml absolute ethanol, 0.5 ml piperidine (freshly distilled), 0.02 ml (1 drop) glacial acetic acid and a few pieces of anti-bumping clips into a dry 50 ml round bottom flask. Provide the flask with a double wall reflux condenser (water-cooled) ; and instal either a $CaCl_2$-guard tube or a cotton plug at the open-end of the reflux condenser so as to prevent the reaction mixture from absorbing atmospheric moisture.

(2) Reflux the reaction mixture over a water-bath for 2 hours and subsequently transfer the contents into a 250 ml Erlenmeyer flask. Add to it 35 ml of cold water and cool the solution in an ice-bath.

(3) Filter the crystalline product in a Büchner funnel, and wash the crystals twice with 3 ml portions of chilled 50% (v/v) aqueous ethanol.

The yield of crude product is 6.7 g mp 92-93°C.

Note. *The crude product is sufficiently pure and can be used directly for the preparation of coumarin-3-carboxylic acid. However, it may be recrystallized from a mixture of ethanol and water (3 : 5).*

Step II. Preparation of Coumarin-3-carboxylic Acid :

(1) Transfer into a 150 ml Erlenmeyer Flask 4 g 3-carbethoxycoumarin, 20 ml ethanol, 10 ml DW and 4 g KOH pellets. Add to it a few pieces of anti-bumping stones and heat the resulting mixture over an electric water-bath until the *'ester'* has undergone complete dissolution. Extend the heating process for an additional period of 15 minutes at a slow and gentle boil.

(2) Prepare a dilute solution of HCl by the addition of 10 ml concentrated HCl to 50 ml water (approx. 2N HCl). Now, start pouring the *warm hydrolysis reaction mixture* into the above acidic solution in small lots at intervals with constant vigorous stirring. Allow the resulting reaction mixture to cool in an ice-bath to get the crystals of the desired product.

(3) Filter the crystals of coumarin-3-carboxylic acid in a Büchner funnel and wash the product with two 15 ml portions of chilled water. Dry the product in between the folds of filter paper, and finally dry it in an oven at 110°C.

The yield of the product is 2.79 g, mp 186.5–188°C (dec.).

4.8.6.6 Precautions

(1) A drop of acetic acid added to the condensation reaction mixture helps in improving the yield of 3-carbethoxy-coumarin. This is due to the formation of the corresponding salt *piperidinium acetate* which being a weakly acidic salt substantially improves the esterification and hence to improve the yield of 3-cabethoxycoumarin.

(2) The esterification process *i.e.,* Step-I must be carried out in a perfect dry condition using almost anhydrous reagents to get a pure and better yield of the product.

(3) Always pour the warm hydrolysis reaction mixture (Step-II) into the acidic solution and not *vice-versa* so as to get a better yield of coumarin-3-carboxylic acid.

4.8.6.7 Recrystallization. The crude product may be recrystallized from water, filtered, air-dried and finally in an oven maintained at 110°C. The yield of the pure product is 2.5 g, mp 188°C (decomposition).

4.8.6.8 Theoretical Yield/Practical Yield. The theoretical yield is calculated from the equation under theory (section 4.8.6.3) as stated below :

218 g of Carbethoxycoumarin on reaction with KOH followed by hydrolysis yields coumarin-3-carboxylic acid = 190.16. g

$\therefore$ 4 g of carbethoxycoumarin shall yield coumarin-3-carboxylic acid $= \frac{190.16}{218} \times 4 = 3.4$ g

Hence, Theoretical yield of coumarin-3-carboxylic acid = **3.4 g**

Reported Practical yield = 2.79 g

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{2.79}{3.49} \times 100 =$ **79.94**

4.8.6.9 Physical Parameters. Coumarin-3-carboxlic acid is obtained as needles from water having mp 188°C (decomposes). It is found to be slightly soluble in water ; soluble in ethanol, alkalies ; and insoluble in either, benzene, and petroleum ether.

4.8.6.10 Uses

(1) Many 3-substituted derivatives of 4-hydroxycoumarin are powerful blood anticoagulants and are mostly used as drugs to control blood clotting.

(2) They are employed as rodenticides, which cause death by haemorrhage.

(3) It is used as a pharmaceutical aid (flavouring agent).

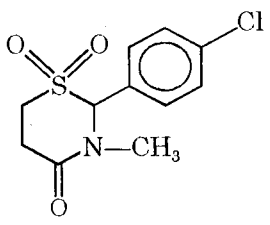
4.8.6.11 Questions for *Viva-Voce*

(1) How will you differentiate 3-carbethoxycoumarin and coumarin-3-carboxylic acid on the basis of their IR-spectrum ? Explain.

(2) Why the cyclic ester (lactone) of coumarin-3-carboxylic acid is readly formed upon acidification of the tri-potassium salt of the *ortho*-hydroxybenzylidenemalonic acid ? Explain.

4.8.7 Chlormezanone

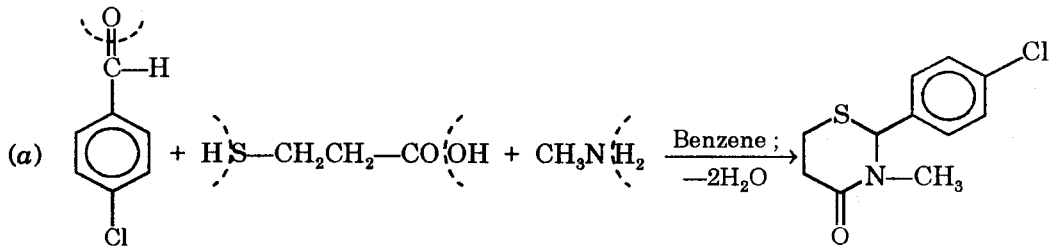
4.8.7.1 Chemical Structure



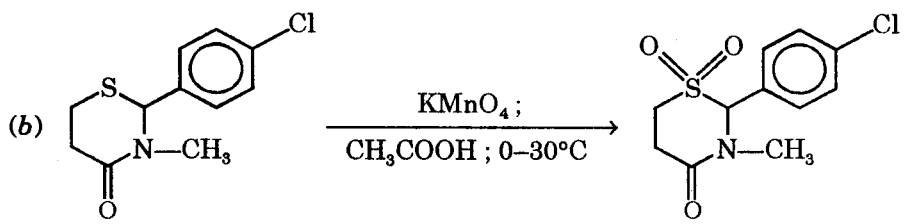
Chlormezanone

4.8.7.2 Synonyms. 2-(4-Chlorophenyl)-3-methyl-4-metathiazanone ; Chloromethazanone ; 2-(4-Chlorophenyl)-3-methyl-4-metathiazanone-1, 1-dioxide.

4.8.7.3 Theory



4-Chloro-benzaldehyde | β-Mercaptopropionic acid | Methyl amine | 2-(4-Chlorophenyl)-3-methyl-4-metathiazanone



2-(4-Chlorophenyl)-3-methyl-4-metathiazanone (241.74) | Chlormezanone (273.74)

Eq. (*a*) depicts the interaction amongst 4-chlorobenzaldehyde, (3-mercaptopropionic acid and methylamine in the presence of benzene when cyclization of the heterocyclic ring takes place with the elimination of two moles of water to yield 2-(4-chlorophenyl)-3-methyl-4-metathiazanone.

Eq. (*b*) shows the oxidation of the resulting product with $KMnO_4$ in the presence of acetic acid between 0–30°C to produce the corresponding 1, 1-dioxide derivative *i.e.,* chlormezanone.

4.8.7.4 Chemicals Required

For Step I. 4-Chlorobenzaldehyde : 14 g ; β-Mercaptopropionic Acid : 10.6 g ; Methyl amine : 3.1 g ; Dilute Ammonia Solution : q.s. ; Benzene : 50 ml.

For Step II. Potassium Permanganate : 11.2 g ; 2-(4-Chlorophenyl-3-methyl-4-metathiazanone : 10 g ; Glacial Acetic Acid : 50 ml ; Sodium bisulphite (saturated solution) : q.s. ; Chloroform ; 100 ml ; Isopropyl Alcohol : q.s. ;

4.8.7.5 Procedure. The synthesis of chlormezanone is usually accomplished in *two* steps, namely :

Step I. Preparation of 2-(4-Chlorophenyl)-3-methyl-4-metathiazanone :

(1) Transfer 14 g chlorobenzaldehyde, 10.6 g β-mercaptopropionic acid and 3.1 g of methyl amine into 100 ml round bottom flask. The reaction mixture is duly refluxed in benzene for 45–50 minutes ; and the water (*i.e.,* products of reaction) is suitably removed from an overhead separator.

(2) The resulting reaction mixture was cooled, washed carefully with dilute ammonium hydroxide followed by water ; and the entire benzene was duly distilled off under reduced pressure.

(3) The oily residue was taken up in ether when the crude 2-(4-chlorophenyl)-3-methyl-4-metathiazanone crystallized out. The crude precipitate was recrystallized at least twice from ether to obtain 16.4 g of pure product*.

Step II. Preparation of Chlormezanone :

(1) A solution of 11.2 g potassium permanganate in 100 ml of warm water was added *dropwise* to a well stirred solution (prefereably using a mechanical stirrer) of 10 g 2-(4-chlorophenyl)-3-methyl-4-metathiazanone taken in 50 ml glacial acetic acid.

Note. *As the above reaction is moderately exothermic in nature, hence special care should be taken in the addition of $KMnO_4$ solution in small lots (dropwise) at intervals ; besides, the temperature of the reaction mixture must NOT be allowed to rise beyond 30°C. If need be EXTERNAL COOLING with chilled water may be done to arrest the rise in temperature above 30°C.*

(2) The resulting reaction mixture is treated with an aqueous sodium bisulphate solution to get rid of the manganese dioxide formed in the medium due to the decomposition of $KMnO_4$.

(3) The thick whitish oil that separated was taken up in chloroform, and subsequently washed three to four times with DW. The chloroform was removed completely over an electric water bath by distillation under vacuo. The oily residue got solidified on attaining room temperature.

The yield of the crude product was 5.5 g mp 115–116.5°C.

4.8.7.6 Precautions

(1) In Step I, after refluxing with benzene, the solvent is removed by distillation under vacuo so that first product is obtained in a purer form without any possible denaturation by heat.

(2) Oxidation of product obtained from Step I should be carried out very cautiously and slowly and preferably below 30°C.

(3) As in Step I, the solvent from the end product (chloroform) must be removed under vacuo.

4.8.7.7 Recrystallization. The crude product obtained in Step II may be recrystallized from isopropyl alcohol to obtain beautiful crystals with an yield of 5.2 g, mp 116.2–118.2°C.

4.8.7.8 Theoretical Yield/Practical Yield. The theoretical yield may be calculated from Eq. (*b*) under theory (section 4.8.7.3) as given under :

241.74 g of 2-(4-Chlorophenyl)-3-methyl-4-metathiazanone on oxidation

yields Chlormezanone = 273.44 g

$\therefore$ 10 g of 2-(4-chlorophenyl)-3-methyl-4-metathiazanone shall yield

$$\text{Chlormezanone} = \frac{273.44}{241.74} \times 10 = 11.32 \text{ g}$$

Hence, Theoretical yield of Chlormezanone = **11.32 g**

Reported Practical yield = 5.5 g

*This can be used directly into the next step.

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{5.5}{11.32} \times 100 = \mathbf{48.59}$

4.8.7.9 Physical Parameters. Chlormezanone is obtained as crystals having mp ranging between 116.2–118.2°C. It is found to be soluble in water at 25°C less than 0.25% (w/v) ; in 95% ethanol at 25°C less than 1.0% (w/v).

4.8.7.10 Uses

(1) It is used in the treatment of anxiety disorders (tranquilizer).

(2) It is also employed in painful muscle spasm often encountered in compound preparations with analgesics.

(3) It is invariably used as a skeletal muscle relaxant.

4.8.7.11 Questions for *Viva-Voce*

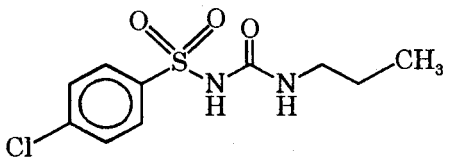
(1) How would you carry out the synthesis of chlormezanone ? Explain.

(2) Why $KMnO_4$ oxidation is done in an acidic medium (CH_3COOH) ? Explain.

(3) How would you separate MnO_2 formed in the reaction mixture ?

4.8.8 Chlorpropamide

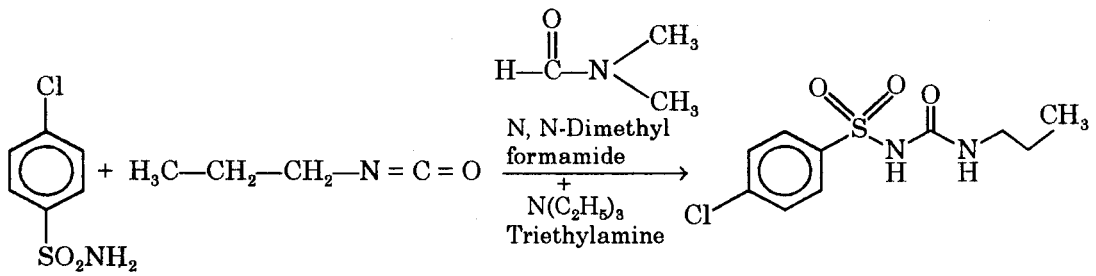
4.8.8.1 Chemical Structure



Chlorpropamide

4.8.8.2 Synonyms. N-Propyl-N'-(*p*-chlorobenzene sulphonyl) urea ; 1-(*p*-Chlorobenzene-sulphonyl) urea ; 1-(*p*-Chlorophenylsulphonyl)-3-propylurea ; 4-Chloro-N-[(propylamino)-carbonyl] benzene-sulphonamide ;

4.8.8.3 Theory



p-Chlorobenzene-sulphonamide (191.62) | Propylisocyanate (85.13) | Chlorpropamide (276.74)

The interaction between *para*-chlorobenzenesulphonamide and propylisocyanate in the presence of N, N-dimethyl formamide (DMF) and triethylamine gives rise to the formation of chlorpropamide. This is a simple condensation reaction whereby one active H-atom from the sulphonamide function gets attached to the N-atom of the isocyanate to result in the formation of the desired product without any loss of an entity separately. However, triethylamine acts as a *'catalyst'* to facilitate the above cited reaction.

4.8.8.4 Chemicals Required. Propyl isocyanate : 13.5 g ; N, N-Dimethylformamide : 15 ml ; Anhydrous *para*-chlorobenzenesulphonamide : 20.25 g ; Anhydrous Triethylamine : 52.5 ml ; Acetic Acid [20% (v/v)] : 1.5 L ; Sodium bicarbonate [5% (w/v)] : 250 ml ; Benzene : 250 ml.

4.8.8.5 Procedure. The various steps involved are given below in a sequential manner :

(1) A solution of 13.5 g (0.64 mol) pure propyl isocyanate in 15 ml anhydrous N, N-dimethylformamide was carefully added into a previously chilled and well-agitated suspension of 20.25 g (0.42 mol) dry *para*-chlorobenzene sulphonamide taken up in 52.5 ml anhydrous triethylamine during the span of 30 to 40 minutes into a 500 ml beaker.

(2) The aforesaid reaction is *mildly exothermic in nature* and, hence was allowed to complete by setting it aside for almost 5 hours at an ambient temperature with occasional stirring in between.

(3) The resulting reaction mixture was then poured into 750 ml cold 20% acetic acid over a period for 60–70 minutes while maintaining a constant agitation throughout the addition being carried out.

(4) Soonafter the addition was complete, the desired product, which had crystallized out, was filtered in a Büchner funnel under suction, washed well with 500 ml of chilled water.

(5) The crude product was dissolved in 250 ml cold 5% sodium carbonate ; and the resulting solution was **immediately filtered from an insoluble gummy substance.** To the clear filtrate was added slowly 750 ml of 20% acetic acid to obtain the precipitate of chlorpropamide.

The yield of the product was 20.47 g mp 128.5–129°C.

4.8.8.6 Precautions

(1) All reagents used in the reaction should be in perfectly dry condition.

(2) As the reaction is mildly exothermic, hence no external heating is required, but the reaction span may be increased upto 5 hours at a stretch to complete the reaction.

(3) The insoluble gummy substance must be removed quickly before acidifying the filtrate with 20% acetic acid to obtain the precipitate of crude chlorpropamide.

4.8.8.7 Recrystallization. The entire crude product (20.47 g) was dried and then subjected to recrystallization from 200 ml dry benzene, to obtain 12.07 g of pure chlorpropamide having mp 129.2–129.8°C.

4.8.8.8 Theoretical Yield/Practical Yield. The theoretical yield is calculated from the equation under theory (section 4.8.8.3) as stated under :

191.62 g of *p*-Chlorobenzene sulphonamide on reacting with

propylisocyanate yeilds Chlorpropamide = 276.74 g

∴ 20.25 g of *p*-Chlorobenzene sulphonamide shall yield

Chlorpropamide $= \frac{276.74}{191.62} \times 20.25 = 29.24$ g

Hence, Theoretical yield of chlorpropamide = **29.24 g**

Reported Practical yield = 20.47 g

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{20.47}{29.24} \times 100 =$ **70**

4.8.8.9 Physical Parameters. Chlorpropamide is obtained as crystals from dilute ethanol mp 127–129°C. It has uv_{max} (0.01 N HCl) : 232.5 nm (ε 16500). Its solubility in water at -pH 6 : 2.2 mg ml^{-1} ; almost insoluble at pH 7.3 ; soluble in ethanol ; moderately soluble in chloroform ; and sparingly soluble in ether, benzene.

4.8.8.10 Uses

(1) It is a hypoglycaemic agent.

(2) It is also sometimes employed in diabetes insipidus.

4.8.8.11 Questions for *Viva-Voce*

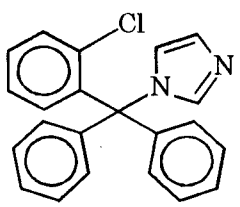
(1) Why is it called a 'sulphonylurea' ?

(2) Can this reaction be termed as 'condensation reaction' ? Explain.

(3) Why is it necessary to have all the reagents in anhydrous conditions ?

4.8.9 Clotrimazole

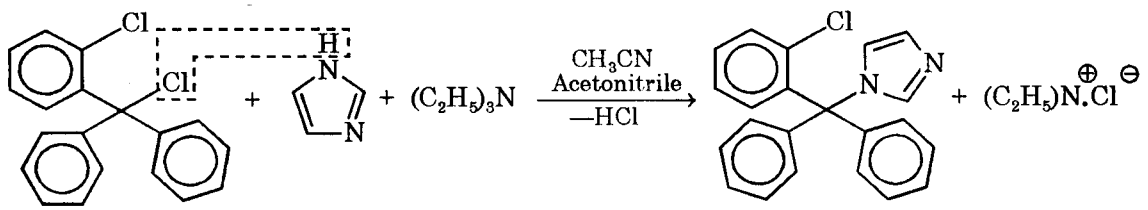
4.8.9.1 Chemical Structure



Clotrimazole

4.8.9.2 Synonyms. 1-[(2-Chlorophenyl) diphenylmethyl]-1H-inidazole ; 1-(*o*-Chlorotrityl) imidazole ; 1-(*o*-Chloro-α, α-diphenylbenzyl) imidazole.

4.8.9.3 Theory



o-Chlorophenyl-diphenylmethyl chloride (313) | Imidazole (68.08) | Triethyl-amine | Clotrimazole (344.84) | Triethylamine hydrochloride

o-Chlorophenyldiphenylmethyl chloride on being treated with imidazole and triethylamine in the presence of acetonitrile loses a mole of hydrogen chloride to produce the desired condensed product clotrimazole. The liberated HCl combines with the triethylamine to form the corresponding hydrochloride salt ; and thereby gets separated from the reaction mixture.

4.8.9.4 Chemicals Required. *o*-Chlorophenyldiphenylmethyl chloride : 15.65 g ; Imidazole : 3.4 g ; Acetonitrile : 50 ml ; Triethylamine : 5.1 g ; Benzene : 100 ml ; Acetone : 100 ml.

4.8.9.5 Procedure

(1) Transfer 15.65 g (0.05 mol) *o*-chlorophenyldiphenyl methyl chloride and 3.4 g imidazole are duly dissolved in 50 ml acetonitrile in a 250 ml beaker with constant stirring, preferably with a magnetic stirrer ; add to it 5.1 g triethylamine and continue the stirring process for 20–30 minutes.

(2) The liberated HCl from the reaction mixture would react promptly the triethylamine to yield the corresponding hydrochloride salt which separates out even at the room temperature. It is filtered.

(3) The reaction mixture is allowed to be heated at 50°C for a duration of 3 hours so as to complete the reaction.

(4) On cooling the above reaction mixture to ambient temperature, 100 ml benzene is added and the reaction mixture is stirred moderately for 10–15 minutes. It is now washed salt-free with water.

(5) The benzene-solution is dried over anhydrous sodium sulphate, filtered and duly concentrated by evaporation on an electric water-bath in an efficient fuming cup-board.

[Caution. Benzene is carcinogenic, hence its fumes must not be inhaled.]

(6) The concentrated solution upon cooling yields 16.7 g crude clotrimazole having mp 154–156°C.

4.8.9.6 Precautions

(1) Triethylamine should be added at the end of the reaction to take up the liberated HCl and form a solid corresponding salt *i.e., triethylamine hydrochloride.*

(2) The benzene should be evaporated only in an efficient fuming cup-board.

4.8.9.7 Recrystallization. The crude clotrimazole is dissolved in the minimum quantity of acetone to obtain the pure crystals of the product upto 11.86 g, mp ranging between 147–149°C.

4.8.9.8 Theoretical Yield/Practical Yield. The theoretical yield is calculated from the equation under theory (section 4.8.9.3) as stated below :

313 g of *o*-Clorophenyldiphenyl-methyl chloride (I) on reacting with

Imidazole yields Clotrimazole = 344.84 g

$\therefore$ 15.65 g of (I) on reacting with imidazole shall yield Clotrimazole

$$= \frac{344.84}{313} \times 15.65 = 17.24 \text{ g}$$

Hence, Theoretical yield of Clotrimazole = **17.24 g**

Reported practical yield = 16.7 g

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{16.7}{17.24} \times 100 = \mathbf{96.86}$

4.8.9.9 Physical Parameters. The crystals of clotrimazole has mp 147–149°C. It is a weak base, slightly soluble in water, benzene, toluene ; soluble in acetone, chloroform, ethyl acetate and DMF. It gets hydrolysed rapidly upon heating in aqueous acids.

4.8.9.10 Uses

(1) It is an antifungal agent used topically in *mucocutaneous candidiasis**, *pityriasis versicolor***, and *dermatophytosis****.

(2) It has also been used occasionally in the treatment of *trichomoniasis***** resistant to other antifungal agents or when other agents are contraindicated.

4.8.9.11 Questions for *Viva-Voce*

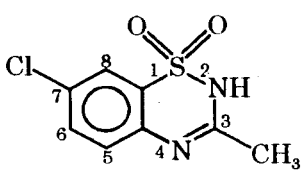
(1) Why is it necessary to add triethylamine in the synthesis of clotrimazole ?

(2) What is the role of 'acetonitrile' as a medium in this synthesis ?

(3) Could you name any two pathogenic fungi for which clotrimazole is recommended as a cure ?

4.8.10 Diazoxide

4.8.10.1 Chemical Structure



Diazoxide

4.8.10.2 Synonyms. 7-Chloro-3-methyl-2H, 1, 2, 4-benzothiadiazine 1, 1-dioxide ; 3-Methyl-7-chloro-1, 2, 4-benzothiadiazine 1, 1-dioxide.

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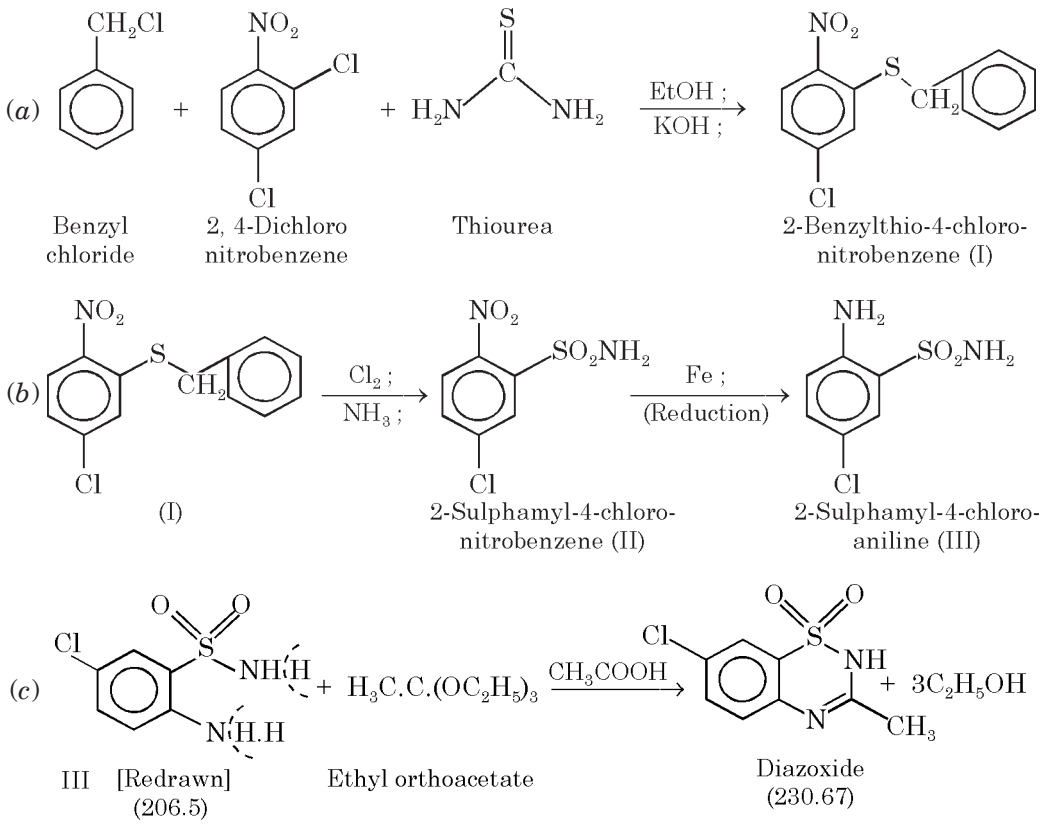
*Infection concerning mucous membrane and the skin caused by any species of *Candida*, but chiefly *Candida albicans* ; localized in the skin, nails, mouth, vagina, vulva, bronchi or lungs, but may invade the blood stream.

**A fungus infection of the skin producing yellow or fawn-coloured branny patches.

***A fungus infection of the skin of the hands and feet esp. between the toes.

****Infestation with a parasite of the genus *Trichomonas, e.g., T. vaginalis* which produces vaginal discharge.

4.8.10.3 Theory



Eq. (*a*) shows the interaction of benzyl chloride, 2-4-dichloronitrobenzene and thiourea to result into the formation of 2-benzylthio-4-chloro-nitrobenzene (I).

Eq. (*b*) depicts how (I) on being treated with Cl_2-gas followed by ammonia produces the 2-sulphamyl-4-chloro-nitrobenzene (II) ; which upon reduction with iron filings yields the corresponding 2-Sulphamyl-4-chloroaniline (III).

Eq. (*c*) illustrates the interaction of (III) with ethyl ortho-acetate in the presence of acetic acid to obtain the desired compound, diazoxide, with the elimination of three moles of ethanol.

4.8.10.4 Chemicals Required. Benzyl chloride : 63 g ; Thiourea : 38 g ; Conc. Ammonia Soln. : 3 drops ; 2, 4-Dichloronitrobenzene : 96 g ; Ethanol : 200 ml ; Ethanolic KOH Soln. (70 g in 500 ml EtOH) : 500 ml ; 2-Benzylthio-4-chloronitrobenzene : 5 g ; Aq. Acetic Acid [33% (v/v)] 1 L ; Chloroform : 1.5 L ; Anhydrous Sodium Sulphate : q.s. ; Liquid Ammonia : 400 ml ; *n*-Hexane : q.s. ; Methanol : q.s. ; Ammonium chloride : 4.4 g ; 2-Sulphamyl-4-chloro-nitrobenzene : 3 g ; Iron Fillings : 4.4 g ; 2-Sulphamyl-4-chloroaniline : 6 g ; Ethyl orthoacetate : 15 ml.

4.8.10.5 Procedure. The various steps involved are given below in a sequential manner :

(1) Mix 63 g benzyl chloride, 38 g thiourea, 3 drops concentrated NH_4OH solution, and 250 ml [95% (v/v)] ethanol into a 2L round bottom flask fitted with a double-surface reflux condenser. Reflux the reaction mixture for 3 hours and allow it to cool.

(2) Add to the resulting solution 96 g 2, 4-dichloro-nitrobenzene in 200 ml ethanol. Heat the mixture to reflux and then add drop-wise a solution of 500 ml ethanolic KOH solution. Continue the refluxing for another 2 hours, cool the contents, filter the solid product in a Büchner funnel under suction, wash with aqueous ethanol and dry between the folds of filter paper. The product thus obtained is 2-benzylthio-4-chloro-nitrobenzene (I).

(3) Suspend 50 g of (I) obtained in step (2) in 1 L of 33% aqueous acetic acid. Pass pure Cl_2-gas through the suspension by means of gentle bubbling for a span of 2 hours, while strictly maintaining the temperature of the suspension at a low temperature ranging between 0–5°C.

(4) Extract the resulting mixture at least thrice successively with 400 ml each of pure dry chloroform, combine the extracts, and wash the chloroform extract several times with DW. Now, dry the chloroform solution with anhydrous sodium sulphate and filter.

(5) Evaporate the dried chloroform layer under reduced pressure to a residue, add to it 400 ml of liquid ammonia, stir well mechanically in a fuming cup-board ; and allow the excess ammonia to evaporate completely. Triturate the residue with *n*-hexane to form a crystalline solid, continue trituration with water and subsequently filter the solid to yield sufficiently pure 2-sulphamyl-4-chloro-nitrobenzene (II).

[**Note :** *The product (II) may be recrystallized from aqueous MeOH.*]

(6) Transfer to a 250 ml round bottom flask 4.4 g ammonium chloride, 18 ml methanol, 9 ml water, and 3 g of (II) obtained from step (5). Reflux the resulting mixture gently, while adding from the top-end of the condenser 4.4 g iron fillings in small lots at intervals during a period of 90–100 minutes. Cool the mixture and filter the solid product at the pump. Recrystallize the crude product from minimum quantity of aqueous methanol to yield substantially pure 2-sulphamyl-4-chloroaniline (III).

(7) Heat a mixture of 6 g (III) and 15 ml ethyl orthoacetate at 100–110°C for a period of 90–100 minutes. Cool, the contents to obtain the desired crude product, diazoxide, filter at the pump and drain well.

The yield of the crude product is 5.32 g having mp 329–330.5°C.

4.8.10.6 Precautions

(1) In step (3) the chlorine gas must be passed through the suspension slowly and strictly at a temperature between 0–5°C.

(2) In step (5) the introduction of 400 ml of liquid ammonia into the chloroform evaporated residue obtained from step (4) must be done very cautiously in an efficient fuming cup-board.

(3) In step (6) the addition of *iron-fillings* into the refluxing reaction mixture is to be carried out over a span of 90–100 minutes in small lots at intervals.

4.8.10.7 Recrystallization. The crude diazoxide is dissolved in minimum amount of aqueous ethanol (1 : 1) to obtain white crystalline mass 5.1 g having mp 329.5–330°C.

4.8.10.8 Theoretical Yield/Practical Yield. The theoretical yield is calculated from the equation under theory (section 4.8.10.3) as stated under :

206.5 g of 2-Sulphamyl-4-chloro-aniline (III) on treatment with Ethyl orthoacetate yields Diazoxide = 230.67 g

$\therefore$ 6 g of (III) shall yield Diazoxide $= \frac{230.67}{206.5} \times 6 = 6.70$ g

Hence, Theoretical yield of Diazoxide = **6.70 g**

Reported Practical yield = 5.32 g

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{5.32}{6.70} \times 100 =$ **79.4**

4.8.10.9 Physical Parameters. Diazoxide is obtained as crystals from dilute alcohol having mp 330–331°C. It has uv_{max} (methanol) : 268 nm (ε11300). It is found to be soluble in ethanol and alkaline solutions ; and practically insoluble in water.

4.8.10.10 Uses

(1) It is a direct acting peripheral vasodilator which reduces blood pressure (anti-hypertensive).

(2) It also exhibits antidiuretic and hyperglycaemic effects.

4.8.10.11 Questions for *Viva-Voce*

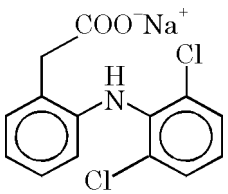
(1) What are the various steps involved in the synthesis of diazoxide ? Explain.

(2) Can diazoxide be prepared from an '*alternative route*' ?

(3) What is the mode of action of diazoxide as an 'antihypertensive' agent ?

4.8.11 Diclofenac Sodium

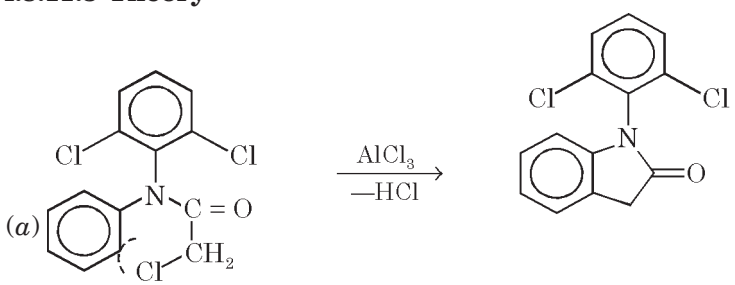
4.8.11.1 Chemical Structure



Diclofenac sodium

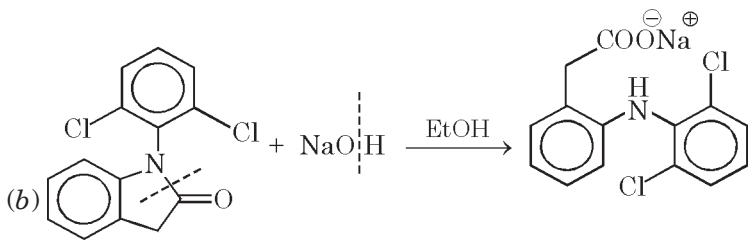
4.8.11.2 Synonyms. 2-[(2, 6-Dichlorophenyl) amino] benzeneacetic acid monosodium salt ; Sodium [*o*-(2, 6-dichlorophenyl) amino] phenyl] acetate.

4.8.11.3 Theory



N-Chloroacetyl-N-phenyl-2, 6-dichloroaniline (I)

1-(2,6-Dichlorophenyl)-2-indolinone (II)



(II)
(242.5)

Diclofenac sodium
(318.13)

Eq. (*a*) shows the interaction between N-chloroacetyl-N-phenyl-2, 6-dichloroaniline (I) and anhydrous aluminium chloride whereupon the indolin ring closure occurs to yield 1-(2, 6-dichlorophenyl)-2-indolinone (II) with the elimination of a mole of HCl.

Eq. (*b*) illustrates the formation of the corresponding sodium salt of diclofenac by treatment of (II) with NaOH in the presence of ethanol when the indolinone ring ruptures as shown with dotted lines to obtain the desired product *i.e.,* dichlofenac sodium.

4.8.11.4 Chemicals Required. N-Chloroacetyl-N-phenyl-2, 6-dichloroaniline : 16 g ; Anhydrous Aluminium Chloride : 16 g ; Chloroform : 200 ml ; 1-(2, 6-Dichlorophenyl)-2-indolinone : 18.6 g ; Ethanol : 66 ml ; NaOH (2N) solution : 66 ml ;

4.8.11.5 Procedure. The various steps involved are as follows :

(1) 16 g each of N-chloroacetyl-N-phenyl-2, 6-dichloroaniline and anhydrous aluminium chloride are thoroughly mixed together and heated gently for a duration of 2 hours at 160°C in a 150 ml round bottom flask.

(2) The resulting melt thus obtained is allowed to cool and poured onto in a thin stream into a 500 ml beaker containing 200 g of crushed ice with constant stirring. The coil which gets separated is dissolved in 200 ml of chloroform. The chloroform layer is subsequently washed with 40 ml of DW ; and dried over sodium sulphate anhydrous and concentrated under 11 torr. The residue thus obtained is distilled and allowed to cool. The intermediate, 1-(2, 6-dichlorophenyl)-2-indolinone (II) is obtained as a solid product mp 126–127°C.

(3) A solution of 18.6 g 1-(2, 6-dichlorophenyl)-2-indolinone (II) is made in 66 ml ethanol and 66 ml 2 N NaOH solution into a 250 ml round bottom flask fitted with a reflux condenser for a duration of 4 hours. The resulting solution is allowed to cool at 0–5°C in a refrigerator for at least 4 hours. The crude crystals thus obtained is filtered in a Büchner funnel, washed with a little spray of chilled water, dried in the oven ; 23.2 g having mp 281–283°C.

4.8.11.6 Precautions

(1) The compound (I) and $AlCl_3$ must be heated gently upto 150°C for 2 hours, cooled to ambient temperature and poured onto crushed ice with stirring to obtain product (II).

(2) The product (II) must be treated with dilute NaOH solution and refluxed cautiously for 4 hours before allowing it to be chilled at 0–5°C for another similar span.

4.8.11.7 Recrystallization. The crude product obtained above (23.2 g) is dissolved in minimum amount of water, a few grammes of activated decolourizing carbon may be obtained, filtered and cooled to obtain 22.5 g of recrystallized product mp ranging between 283–285°C.

4.8.11.8 Theoretical Yield/Practical Yield. The theoretical yield is calculated from the Eq. (*b*) under theory (section 4.8. 11.3) as given under :

242.5 g of 1-(2, 6-Dichlorophenyl)-2-indolinone (II) on reacting with NaOH yields

Diclofenac sodium = 318.13 g

$\therefore$ 18.6 g of Compound (II) shall yield Diclofenac sodium

$$= \frac{318.13}{242.5} \times 18.6 = 24.40 \text{ g}$$

Hence, Theoretical yield of Diclofenac Sodium = **24.40 g**

Reported Practical Yield = 23.2 g

Therefore, Percentage Practical yield $= \dfrac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$$= \frac{23.2}{24.4} \times 100 = \mathbf{95.08}$$

4.8.11.9 Physical Parameters. The crystals obtained from water has mp 283–285°C. It exhibits uv_{max} (methanol) 283 nm ($\in$ 1.05 × 10^5) ; phosphate buffer (pH 7.2) 276 nm ($\in$ 1.01 × 10^5). It has solubility at 25°C (mg. ml^{-1}) ; deionized water (ph 5.2) > 9 ; methanol > 24 ; acetone 6 ; acetonitrile < 1 ; cyclohexane < 1 ; HCl (pH 1.1) < 1 ; phosphate buffer (ph 7.2)6. It has dissociation constant pKa 4 ; and partition coefficient (*n*-octanol/aqueous buffer) : 13.4.

4.8.11.10 Uses

(1) It is a non-steroidal antiinflammatory drug (NSAID) and used mainly as its sodium salt for the relief of pain and inflammation in various conditions, such as : musculoskeletal and joint disorders *viz.*, rheumatoid, arthritis, osteoarthritis ; and ankylosing spondolytis ; peri-articular disorders, for instance : bursitis* and tendenitis** ; soft-tissue disorders, such as : sprains and strains ; and other painful conditions, namely : renal colic, acute gout, dysmenorrhoea, and following certain surgical procedures.

(2) It is mostly employed as a broad-based antiinflammatory agent.

Note. The corresponding *'potassium salt' i.e.,* dicolfenac potassium is recommended for patients having hypertension indications (*i.e.,* to avoid sodium ions).

4.11.11 Questions for *Viva-Voce*

(1) How would you accomplish the synthesis of diclofenac sodium in a laboratory ?

(2) Why does the 'potassium-salt' of dichlofenac usually recommended to patients having hypertension ?

---

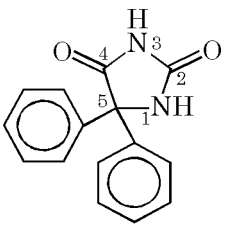
*Inflammation of a bursa, esp. those located between bony prominences and muscle or tendon, as the shoulder and knee.

**An inflammation of a 'tendon'.

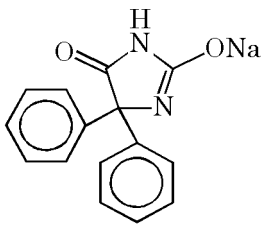
(3) Enumerate at least 10 important uses of Dichlofenac sodium as a potent NSAID.

4.8.12 5, 5-Diphenyl Hydantoin (Phenytoin) Sodium

4.8.12.1 Chemical Structure



Phenytoin



Phenytoin sodium

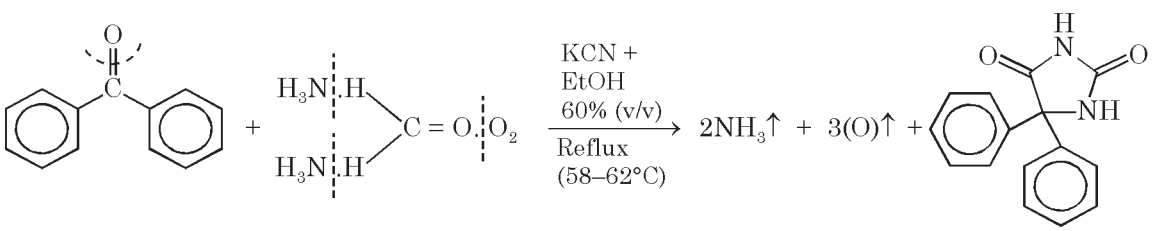
4.8.12.2 Synonyms. 5, 5-Diphenyl-2, 4-imidazolidinedione.

4.8.12.3 Theory. Phenytoin may be prepared from the following *two* different routes of synthesis, namely :

(*a*) Starting from '*benzophenone*', and

(*b*) Starting from '*benzaldehyde*'.

Method I. From Benzophenone :

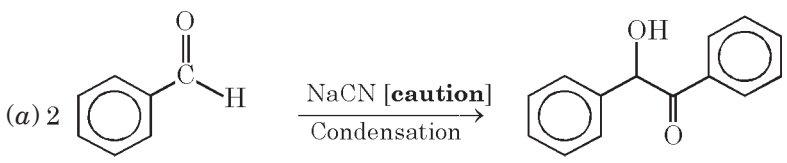


Benzophenone (182.22) | Ammonium carbonate | Ammonia | Nascent oxygen | Phenytoin (252.27)

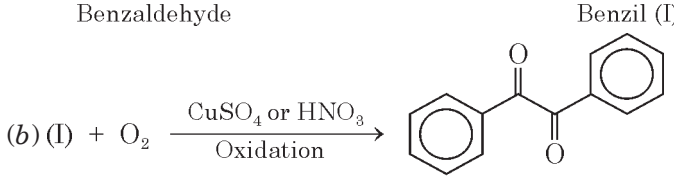
Benzophenone reacts with ammonium carbonate in the presence of KCN and ethanol (60%) to give rise to the formation of one mole of phenytoin by ring closure (imidazoline) and with the elimination of ammonia and nascent oxygen.

Note. Phenytoin being poorly water-soluble is mostly used as its sodium salt by enolization of the imidazoline ring and subsequent treatment with a calculated quantum of NaOH to obtain *Phenytoin Sodium.*

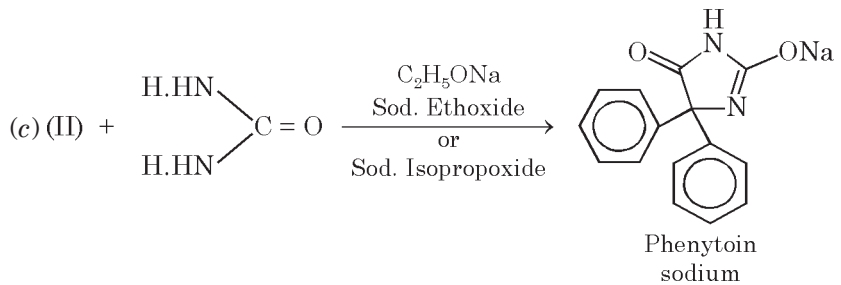
Method II. From Benzaldehyde :



Benzaldehyde | Benzil (I)



Benzoin (II)



Eq. (*a*) : Two moles of benzaldehyde get condensed in the presence of NaCN to yield benzoin (I).

Eq. (*b*) : Benzoin (I) on being subjected to oxidation in the presence of $CuSO_4$ or conc. HNO_3 produces benzil (II).

Eq. (*c*) : Benzil (II) under reaction with urea in the presence of either sodium ethoxide or sodium isopropoxide gives rise to the formation of phenytoin sodium.

However, in the present text the detailed procedure for the synthesis of '*phenytoin*' from benzophenone shall be described (*i.e., Method I*).

4.8.12.4 Chemicals Required. Benzophenone (pure) : 10 g ; Potassium Cyanide **[Caution : Deadly Poison]** : 4 g ; Ammonium carbonate ; 16 g ; Ethanol [60% (v/v)] : 100 ml ; Hydrochloric Acid (6 M) : q.s. ; Sodium Hydroxide Solution (2 M) ; q.s. ; Ethanol [90% (v/v)] = 600 ml.

4.8.12.5 Procedure. The various steps involved are as stated below :

(1) Transfer carefully 10 g benzophenone (1 mol), 4 g potassium cyanide (1.22 mols) [**Caution**], 16 g ammonium carbonate (3.3 mols) into a 250 ml round bottom flask fitted with a double surface reflux condenser. Dissolve the contents of the flask in 100 methanol (60%) and warm under a reflux condenser for a duration of 10 hours between 58–62°C, *preferably without stirring the contents of the flask.*

(2) After warming for 10 hours the flask is subjected to a partial vacuum, and the temperature is raised enough so as to allow concentration of the reaction mixture to almost *two-thirds* of the original volume.

(3) Acidify the contents of the flask at room temperature, with a slight excess of hydrochloric acid using litmus paper. The contents of the flask is chilled adequately to obtain a solid product (hydantoin) which is filtered off in a Büchner funnel under suction and washed with a spray of chilled water.

(4) The hydantoin obtained in (3) is subsequently treated with an aqueous solution of dilute sodium hydroxide solution to dissolve it from the solid residue of **unreacted benzophenone.** After filtration, the resulting alkaline extract is then acidified carefully to cause the separation of solid pure phenytoin sodium which is filtered off and dried at 100°C in an electric oven.

The yield of the product is 12.7 g, mp 293–296°C.

Note : In case, the time of warming the 'reaction mixture' is enhanced by 3 to 4 times, almost 100% net yields are obtained.

4.8.12.6 Precautions

(1) KCN must be used with UTMOST PRECAUTIONS as it is a deadly **POISON.**

(2) While warming the flask for 10 hours under reflux, care should be taken *not to stir the contents at all.*

(3) The *'unreacted benzophenone'* must be removed from the phenytoin sodium as far as possible to avoid its contamination.

4.8.12.7 Recrystallization. The product may be recrystallized from ethanol having mp 295–298°C.

4.8.12.8 Theoretical Yield/Practical Yield. The theoretical yield is calculated from the equation under theory (section 4.8.12.3) as stated below :

182.22 g Benzophenone on reacting with Ammonium Carbonate

yields Phenytoin = 252.27 g

$\therefore$ 10 g Benzophenone shall yield Phenytoin $= \dfrac{252.27}{182.22} \times 10 = 13.84$ g

Hence, Theoretical yield of Phenytoin = **13.84 g**

Reported Practical yield = 12.7 g

Therefore, Percentage Practical yield $= \dfrac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \dfrac{12.7}{13.84} \times 100 =$ **91.76**

4.8.12.9 Physical Parameters. Phenytoin is obtained as a powder having mp 295–298°C. It is almost insoluble in water ; 1 g dissolves in about 60 ml ethanol ; 30 ml acetone ; and soluble in alkali hydroxides.

4.8.12.10 Uses

(1) It is one of the drugs of choice for the management of generalized tonic-clonic (grand mal) seizures, complex partial (temporal lobe ; psychomotor) seizures ; and simple partial (focal, Jacksonian) seizures.

(2) Parenterally, it is used for the control of status epilepticus of the generalized grand-mal type ; and also in the control and management of seizures taking place during neurosurgery.

(3) IV phenytoin may be useful in the treatment of paroxysmal atrial tachycardia, ventricular tachycardia and digitalis-induced cardiac arrythmias.

Mechanism. Phenytoin acts on the motor cortex where it stabilizes the neuronal membrane and inhibits the spread of the seizure discharge.

4.8.12.11 Questions for *Viva-Voce*

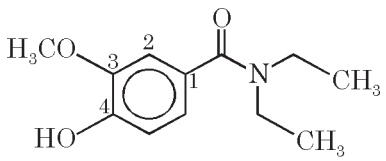
(1) What are the two different routes of synthesis for phenytoin ?

(2) How would you prepare the soluble 'Phenytoin Sodium' from Phenytoin ? Explain the mechanism of reaction involving *keto-enol* tautomerism.

(3) How one may achieve 100% practical yield of '*Phenytoin*' starting from Benzophenone ?

4.8.13 Ethamivan

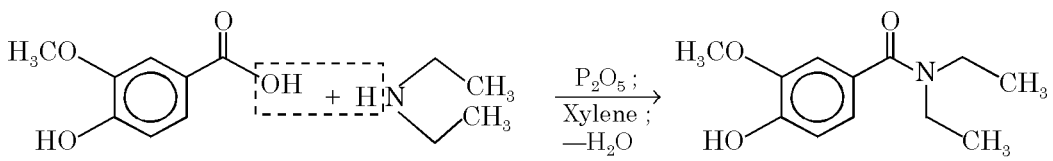
4.8.13.1 Chemical Structure



Ethamivan

4.8.13.2 Synonyms. N, N-Diethylvanillamide ; N, N-Diethyl-4-hydroxy-3-methoxy benzamide ; Vanillic acid diethylamide ; Vanillic diethylamide ;

4.8.13.3 Theory



Vanillic acid (168.15) | Diethyl amine (73.14) | Ethamivan (223.27)

The interaction of vanillic acid and diethylamine in the presence of phosphorus pentoxide in a medium of xylene gives rise to ethamivan with the elimination of one mole of water.

4.8.13.4 Chemicals Required. Vanillic Acid : 4 g ; Diethylamine : 3.6 g ; Phosphorus pentoxide : 2.2 g ; Xylene : 50 ml ; Glass Powder : q.s. ; Potassium Carbonate [2% (w/v)] = 25 ml ; Ether : 50 ml ; Ligroin : 40 ml.

4.8.13.5 Procedure. The various steps involved are enumerated below sequentially :

(1) Transfer 4 g vanillic acid (0.0238 mol) into a 100 ml round bottom flask fitted with a reflux condenser ; and add to it 3.6 g diethylamine (0.05 mol). The reaction being exothermic in nature requires essential cooling. Now, to the cooled reaction mixture add 2.2 g (0.015 mol) P_2O_5 together with 2.2 g glass powder and 25 ml xylene to obtain a thin-paste.

(2) The reaction mixture is boiled for several hours under reflux condenser while the water generated by the reaction gets excluded.

(3) Decantation follows, and the residue is dissolved with the help of a warm solution of potassium carbonate until only glass powder or small amount of impurities remain undissolved, and then the xylene solution is shaken up therewith.

(4) The resulting xylene layer is separated with a separating funnel ; the aqueous layer thus obtained is successively extracted with ether and the combined ethereal layer is mixed with the xylene fraction obtained previously.

(5) The resulting mixture of solvents (*i.e.,* ether + xylene) is subjected to distillation under a very high vacuo (~ 10 Torr) and collecting the fraction between 170–250°C ; and *purifying it further by fractionation.*

(6) A slightly pale yellowish oil is obtained which gets crystallized after a little while.

The crude product is 3.9 g having mp 94.5–95°C.

4.8.13.6 Precautions

(1) Phosphorus pentoxide (P_2O_5) must be added to the cooled reaction mixture.

(2) The reaction mixture is boiled gently under reflux for several hours (5 to 6 hours) and during this process the water molecule formed in the reaction gets eliminated completely.

(3) The organic layer must be distilled at ~ 10 Torr reduced pressure to get a better yield and a purer product.

4.8.13.7 Recrystallization. The crude product is recrystallized by dissolving it in a minimum quantity of *ligroin* to obtain beautiful needles 3.75 g mp 95–95.5°C.

4.8.13.8 Theoretical Yield/Practical Yield. The theoretical yield is calculated from the equation under theory (section 4.8.13.3) as stated below :

168.15 g Vanillic Acid on treatment with Diethylamine

produces Ethamivan = 223.27 g

$\therefore$ 4 g Vanillic Acid shall yield Ethamivan $= \frac{223.27}{168.15} \times 4 = 5.31$ g

Hence, Theoretical yield of Ethamivan = **5.31 g**

Reported Practical yield = 3.9 g

Therefore, Percentage Practical yield $= \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$

$= \frac{3.9}{5.31} \times 100 =$ **73.45**

4.8.13.9 Physical Parameters. Ethamivan is obtained as needles from ligroin having mp ranging between 95–95.5°C.

4.8.13.10 Uses

(1) It has been used as a respiratory stimulant.

(2) It is also given in preparations for the treatment of cerebrovascular and circulatory disorders and hypotension.

4.8.13.11 Questions for *Viva-Voce*

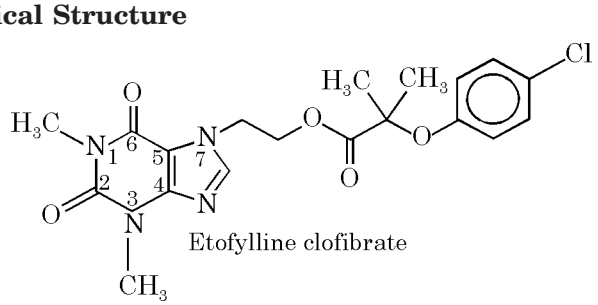
(1) Why is it necessary to add P_2O_5 in this synthesis ?

(2) How would you synthesize '*Ethamivan*' starting from vanillic acid ?

(3) Why is it recommended to distill the organic solvents at a very low reduced pressure ? Explain.

4.8.14 Etofylline Clofibrate

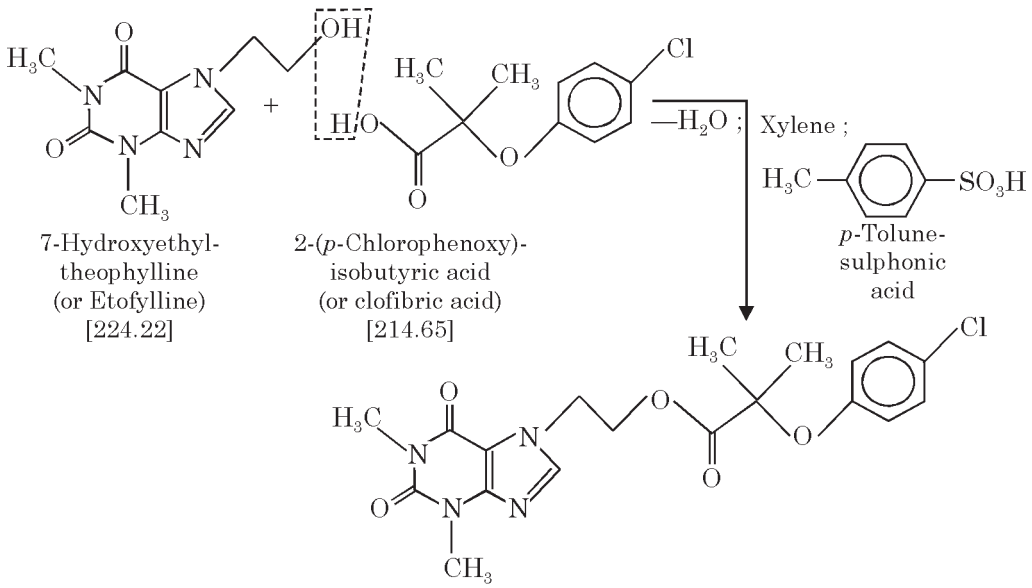
4.8.14.1 Chemical Structure



Etofylline clofibrate

4.8.14.2 Synonyms. Theofibrate ; 1-(Theophyllin-7-yl) ethyl-2-(*p*-chlorophenoxy) isobutyrate ; 2-(4-Chlorophenoxy)-2-methyl propionic acid 2-(1, 2, 3, 6-tetrahydro-1, 3-dimethyl-2, 6-dioxo-7H-purin-7-yl) ethyl ester ;

4.8.14.3 Theory



Etofylline interacts with clofibric acid in the presence of *p*-toluene sulphonic acid in a medium of xylene to give rise to the formation of etofylline clofibrate with the elimination of a mole of water. However, the presence of *p*-toluene sulphonic acid acts as a felicitator in the abstraction of a mole of water to obtain the corresponding desired ester.

4.8.14.4 Chemicals Required. 2-(*p*-Chlorophenoxy) isobutyric acid = 10.73 g ; 7-Hydroxy ethyltheophylline : 5.6 g ; *p*-Toluene sulphonic acid = 0.15 g ; Sodium bicarbonate solution (0.5 M) : 50 ml ; Isopropanol : 50 ml ; Xylene : 25 ml.

4.8.14.5 Procedure. The various steps involved are as given below :

(1) Transfer 10.73 g (0.005 mol) 2-(*p*-chlorophenoxy) isobutyric acid and 5.6 g (0.025 mol) 7-hydroxy ethyltheophylline were suspended together in 25 ml xylene in a 100 ml round bottom flask. The resulting mixture was heated together for almost 15 hours at a stretch in a *water-separator* following the addition of 0.15 g *p*-toluenesulphonic acid.

(2) The resulting solution was shaken adequately with dilute sodium bicarbonate solution till it became alkaline to litmus paper, washed with water ; and the solvent was carefully evaporated in a rotary evaporator.

(3) The solid residue thus obtained was filtered in a Büchner funnel under suction, washed with a little chilled water, drained and dried in between the folds of filter paper.

The yield of the crude product is 6.1 g mp 130.5-131.5°C.

4.8.14.6 Precautions

(1) The reaction mixture is heated together for 15 hours in a *water separator*, which can be accomplished by simply placing some **activated sieves*** in the reaction flask, so as to remove the small amount of water formed during the course of reaction (see section 4.8.14.3).

(2) After completion of the reaction, the resulting mixture is carefully made alkaline to litmus paper with sodium bicarbonate solution (0.5 M).

(3) The solvent *i.e.*, Xylene should be removed either under rotary evaporator or under reduced pressure.

4.8.14.7 Recrystallization. The crude product obtained in section 4.8.14.5 is recrystallized from a minimum quantity of isopropanol and subsequent chilling ; thus yielding a pure product 5.8 g having mp ranging between 131-132°C.

4.8.14.8 Theoretical Yield/Practical Yield. The theoretical yield is calculated from the equation under theory (section 4.8.14.3) as given below :

224.22 g Etofylline upon interaction with Clofibric Acid gives rise to

Etofylline clofibrate = 420.85 g

$\therefore$ 5.6 g Etofyline shall yield Etofylline clofibrate $= \frac{420.85}{224.22} \times 5.6 = 10.5$ g

Hence, Theoretical Yield of Etofylline clofibrate = **10.5 g**

Reported Practical Yield = 6.1 g

Therefore, Percentage Practical Yield $= \frac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100$

$= \frac{6.1}{10.5} \times 100 = \mathbf{58}$

4.8.14.9 Physical Parameters. Theofibrate is obtained as colourless crystals from ethanol mp 133-135°C. It is practically insoluble in water at pH 2-7.4 and in cold alcohols. It is, however, found to be soluble in acetone, chloroform and hot alcohols.

4.8.14.10. Uses

(1) It is used as a hypolipidaemic agent in conjunction with dietary modification.

(2) It is employed as antihyperlipoproteinemic.

4.8.14.11 Questions for *Viva-Voce*

(1) How would you synthesize an antihyperlipoproteinemic drug ?

(2) Why is it necessary to remove water from the reaction mixture by the help of '*activated sieves*' in the reaction flask ? Explain.

(3) What is the role of *p*-toluene sulphonic acid in this synthesis ? Explain.

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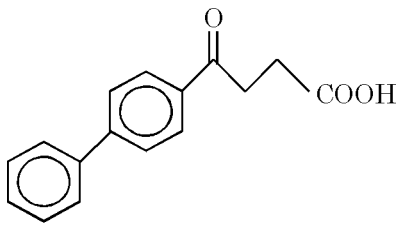
*Leonard *et. al.* '*Advanced Practical Organic Chemistry*', Blackie Academic and Professional, London, 2nd edn., 1995, p-170.

4.8.15 Fenbufen

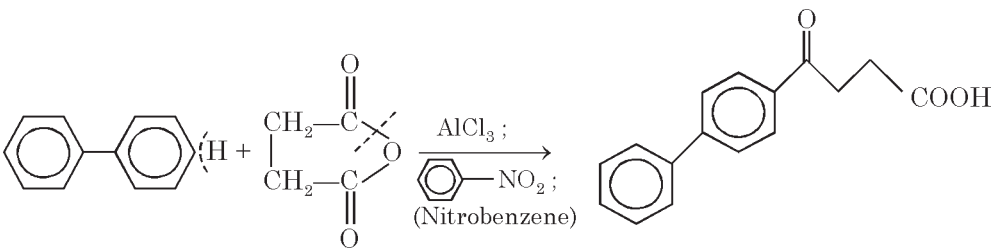
4.8.15.1 Chemical Structure



Fenbufen

4.8.15.2 Synonyms. 3-(4-Biphenylylcarbonyl) propionic acid ; β-*p*-Phenylbenzoyl propionic acid ; Diphenyl-4-γ-oxo-γ-butyric acid ; 4-(4-Biphenylyl)-4-oxobutyric acid.

4.8.15.3 Theory



Diphenyl (154.21) — Succinic Anhydride (48.0) — Fenbufen (254.29)

The interaction between diphenyl and pure succinic anhydride, in the presence of anhydrous aluminium chloride and nitrobenzene, at below 10°C for a sufficiently long duration gives rise to the formation of *fenbufen*. The mechanism of reaction essentially involves the cleavage of the anhydride and one of the active H-atoms of the phenyl ring at the *para*-position forms the terminal carbonyl function in the desired final product *i.e.*, *fenbufen*.

4.8.15.4 Chemicals Required. Anhydrous Aluminium Chloride : 13.5 g ; Nitrobenzene (freshly distilled) : 50 ml ; Succinic Anhydride : 5 g ; Diphenyl : 7.5 g ; Hydrochloric Acid (12 M): 15 ml ; Sodium Carbonate solution [3% (*w*/*v*)] : 400 ml ; Sulphuric Acid (3M) : q.s. ; Ethanol [96% (*v*/*v*)] : q.s. ;

4.8.15.5 Procedure. The various steps involved are as follows :

(1) 13.5 g of anhydrous aluminium chloride is dissolved in 50 ml nitrobenzene, and the resulting solution is maintained at below 10°C in an ice-bath.

(2) A finely powdered mixture of 5 g (0.05 mol) succinic anhydride and 7.5 g (0.05 mol) diphenyl is now added to the stirred solution while maintaining the temperature of the reaction mixture strictly below 10°C. After thorough agitation of the said reaction mixture it is subsequently held at room temperature (20 ± 2°C) for 96 hours with occasional shaking in between.

(3) The resulting reaction mixture is now poured into a solution of 15 ml concentrated HCl in 100 ml of chilled DW with constant stirring. From this acidified reaction mixture the unreacted nitrobenzene is eliminated by steam distillation.

(4) The solid residue is collected in a Büchner funnel under suction, dissolved in 400 ml of 3% hot Na_2CO_3 solution, clarified ; and reprecipitated by the addition of an excess of 3M-H_2SO_4 solution.

The yield of the crude dried product is 9.9 g mp 184-185.8°C.

4.8.15.6 Precautions

(1) Both aluminium chloride and succinic anhydride must be in perfect anhydrous condition, besides the nitrobenzene should also be freshly steam-distilled.

(2) The entire steps in this synthesis must be carried out initially at a temperature not exceeding 10°C ; and then the agitated reaction mixture held at RT* for 96 hrs.

(3) The unreacted nitrobenzene must be removed by steam distillation as far as possible before proceeding to the final curde product.

4.8.15.7 Recrystallization. The crude product is recrystallized from minimum quantity of ethanol and cooling to obtain 9.45 g of pure product, mp ranging between 185-187°C.

4.8.15.8 Theoretical Yield/Practical Yield. The theoretical yeild is calculated from the equation under theory (section 4.8.15.3) as stated under :

154.21 g Diphenyl on reaction with succinic anhydride in the presence of aluminium chloride/nitrobenzene yields Fenbufen = 254.29 g

$\therefore$ 7.5 g Diphenyl shall yield Fenbufen $= \dfrac{254.29}{154.21} \times 7.5 = 12.37$ g

Hence, Theoretical Yield of Fenbufen = **12.37 g**

Reported Practical Yield = 9.9 g

Therefore, Percentage Practical Yield $= \dfrac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100$

$= \dfrac{9.9}{12.37} \times 100 =$ **80.03**

4.8.15.9 Physical Parameters. Fenbufen is obtained as crystals from ethanol having mp 185-187°C.

4.8.15.10 Uses

(1) It is a non-steroidal anti-inflammatory (NSAID) drug.

(2) It is invariably indicated for the relief of pain and inflammation associated with musculoskeletal and joint disorders, for instance : rheumatoid arthritis, osteoarthritis, and ankylosing spondolytis.

4.8.15.11 Questions for *Viva-Voce*

(1) How would you synthesize Fenbufen from diphenyl and succinic anhydride ? Explain.

(2) Why do we add $AlCl_3$ and nitrobenzene in this reaction ? Explain.

(3) What is the necessity of removal of unreacted nitrobenzene from the reaction mixture before proceeding for the recovery of Fenbufen ?

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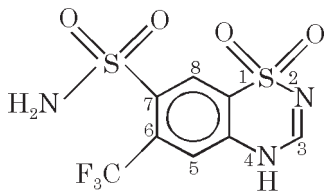
*RT = Room temperature

4.8.16. Flumethiazide

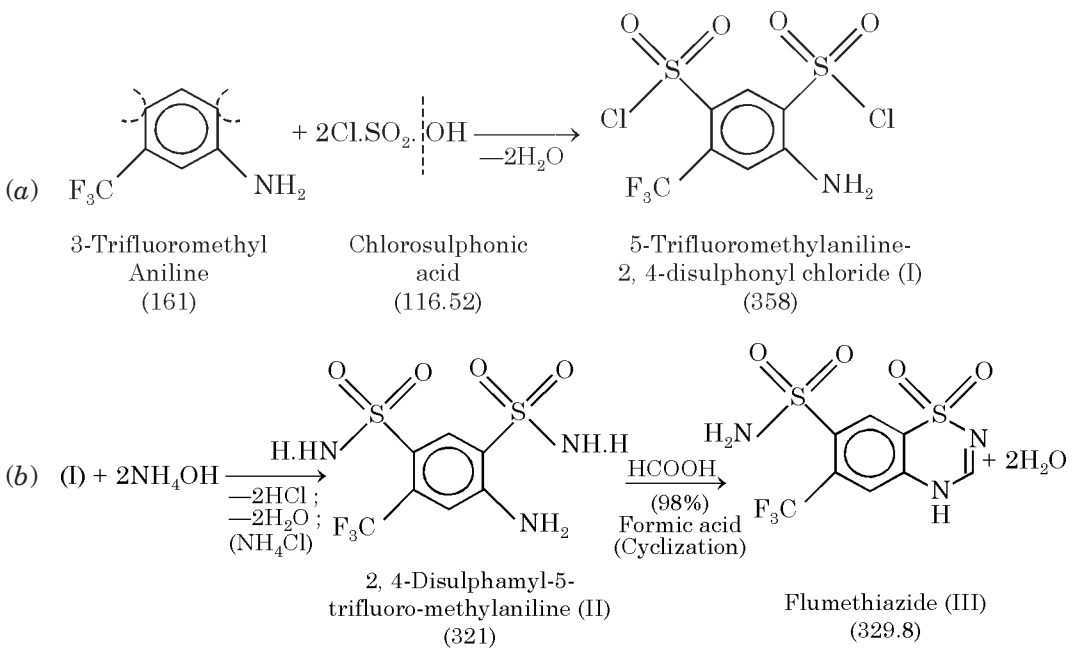
4.8.16.1 Chemical Structure



Flumethiazide

4.8.16.2 Synonyms. 6-Trifluoromethyl-7-sulphamyl-1, 2, 4-benzothiadiazine 1,1-dioxide ; Trifluoromethylthiazide.

4.8.16.3 Theory



Eq. (*a*) illustrates the reaction between 3-trifluoromethyl aniline with two moles of chlorosulphonic acid to form one mole of 5-trifluoromethylaniline-2, 4-disulphonyl chloride (I) with the elimination of two moles of water as indicated above. The amino moiety being *ortho*- and *para*-directing yields compound (I) which is an intermediate.

Eq. (*b*) shows the interaction of (I) with ammonium hydroxide to form the corresponding sulphamyl derivative ; 2, 4-disulphamyl-5-trifluoro-methyl aniline (II) with the elimination of 2 moles each of HCl and H_2O. Further, intermediate compound (II) on being treated with formic acid (98%) gives rise to the desired product, flumethiazide (III), due to '*cyclization*' of the thizadiazine nucleus plus two moles of water get eliminated.

4.8.16.4 Chemicals Required. 3-Trifluoromethyl aniline : 32.2 g ; Chloro-sulphonic Acid (d_4^{20} 1.753) : 150 ml (85.57 g) ; Sodium Chloride : 140 g ; Ether : 200 ml ; Conc. Ammonia solution : 75 ml ; Formic Acid (98%) : q.s. ; Ethanol : 200 ml. ;

4.8.16.5 Procedure

The various steps involved are as follows :

(1) Add dropwise 32.2 g (0.2 mol) 3-trifluoromethylaniline, chilled to 0–5°C, onto 150 ml chlorosulphonic acid taken in a 500 ml beaker with constant stirring and cooling (0–10°C) over a time period of 45–60 minutes.

Note. Care must be taken that the temperature of the reaction mixture should not exceed beyond 10°C in any case. The reaction is highly exothermic in nature.

(2) The ice-bath is removed and 140 g sodium chloride is added in small bits at intervals over a span of 3 hours.

(3) The resulting mixture is heated gradually on a water bath for 30 minutes ; and then slowly upto 160°C on a hot plate over a span of 6 hours with frequent stirring occasionally.

(4) The reaction mixture is cooled and diluted with 500 ml of an ice water slurry and subsequently taken up in ether in successive quantities several times.

(5) The combined ethereal layer is filtered, evaporated to dryness (in a fuming cup-board over an electric water-bath) to obtain 5-trifluoromethylaniline-2, 4-disulphonyl chloride (I).

(6) The crude residue (I) is heated on the steam-bath for 60 mts. with 75 ml of conc. ammonium hydroxide. The reaction mixture is chilled and filtered to yield 2, 4-disulphamyl-5-trifluoromethylaniline (II) having mp ranging between 241–243°C.

(7) The resulting intermediate product (II) is finally treated with an excess of 98% formic acid and maintained at steam-bath temperature for a duration of 3 hours. Subsequent evaporation and careful dilution with water gives rise to the desired product, flumethiazide, (III).

4.8.16.6 Precautions

(1) The first step must be carried out with extreme precaution as the reaction is EXOTHERMIC in nature.

(2) The addition of solid NaCl gradually over 3 hours in step (2) specifically facilitates the formation of the corresponding disulphonyl chloride salt (I).

(3) Step (6) *i.e.,* amination with conc. NH_4OH must be carried out in an efficient fuming cup-board.

(4) Finally, the treatment with formic acid and subsequent heating on a steam bath for 3 hours is an absolute necessity to obtain the desired product (III).

The yield of the crude product is 48.5 g mp 304-308 °C.

4.8.16.7 Recrystallization. The crude product is dissolved in minimum quantity of ethanol to obtain the recrystallized pure flumethiazide 45.5 g having mp 305–307.8°C.

4.8.16.8 Theoretical Yield/Practical Yield. The theoretical yield is calculated from the equation given under theory (section 4.8.16.3) as stated below :

161 g of 3-Trifluoromethylaniline on reaction with chlorosulphonic

Acid/Ammonia/Formic Acid forms Flumethiazide = 329.28 g

∴ 32.2 g of 3-Trifluoromethylaniline shall

$$\text{yield Flumethiazide} = \frac{329.28}{161} \times 32.2 = 65.86 \text{ g}$$

Hence, Theoretical Yield of Flumethiazide = **65.86 g**

Reported Practical Yield = 48.5 g

$$\text{Therefore, Percentage Practical Yield} = \frac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100$$

$$= \frac{48.5}{65.86} \times 100 = \mathbf{73.64}$$

4.8.16.9 Physical Parameters. The crystals of flumethiazide get decomposed at 305.4 – 307.8°C, and uv_{max} : 278 nm ($E^{1\%}_{1cm}$ 335)(50% diglyme + 50% 0.1 NHCl). It is found to be soluble in water (50 mg ml^{-1} in boiling water with decomposition), and soluble in ethanol, methanol and DMF. It is almost insoluble in ethyl acetate, methyl ethyl ketone, benzene and toluene. It is unstable in alkaline solution whereby it gets converted to its precursor α, α, α-trifluoro-3-amino-4,6-disulfamoyltoluene.

4.8.16.10 Uses

(1) It is a potent carbonic anhydrase inhibitor.

(2) It is a thiazide diuretic useful in the management of edema associated with *cardiac failure, hepatic cirrhosis, premenstrual tension, and steroid administration.*

(3) It is also recommended for the tratment of mild to moderate hypertension.

4.8.16.11 Questions for *Viva-Voce*

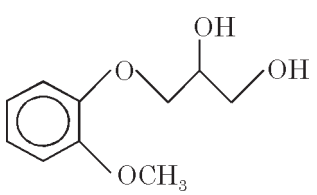
(1) How does formic acid help in the cyclization of 2,4-disulphamyl-5-trifluoro-methylaniline to form flumethiazide ?

(2) Why flumethiazide is 'unstable' in alkaline medium ? Explain.

(3) How do we get NH_4Cl in the reaction mixture after the amination of the corresponding disulphonyl chloride salt (I) ? Explain.

4.8.17 Guaifensin

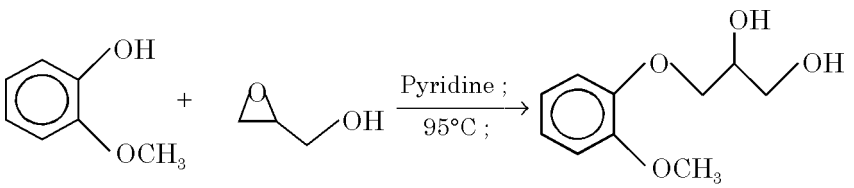
4.8.17.1 Chemical Structure



Guaifensin

4.8.17.2 Synonyms. 3-(2-Methoxyphenoxy)-1, 2-propanediol ; Guaiacyl glyceryl ether ; Glycerol guaicolate ; α-Glyceryl guaiacol ether ; *o*-Methoxyphenyl glyceryl ether ; Guaiphensin ; Guaicuran.

4.8.17.3 Theory



o-Methoxyphenol (124) | Glycidol (74.08) | Guaifensin (198.22)

o-Methoxyphenol and glycidol undergoes condensation, with intermolecular rearrangement, in the presence of pyridine at 95°C to give rise to the formation of guaifensin.

Note. The above reaction is highly exothermic in nature and hence special care must be taken not to allow the temperature to rise beyond 110°C in any case whatsoever, to get a pure and better yield of the desired product, guaifensin.

4.8.17.4 Chemicals Required. *o*-Methoxyphenol : 57 g ; Glycidol : 32 g ; Pyridine : 1 g ; Ethanol : 200 ml.

4.8.17.5 Procedure. The different steps followed sequentially are as stated below :

(1) A mixture of 57 g (0.46 mol) *o*-methoxyphenol, glycidol 32 g (0.43 mol) and 1 g pyridine is warmed in a 500 ml beaker to 95°C, at which temperature a vigorous reaction takes place. Special care must be taken to cool down the reaction mixture so as to prevent the temperature rising above 110°C by all means.

(2) When the exothermic reaction has almost subsided, the resulting reactants are maintained at 95°C for an additional period of 60 minutes in order to complete the reaction.

(3) The reaction mixture is subjected to distillation under reduced pressure ; and the major fraction boiling between the range 176–180°C at 0.5 mm pressure is collected separately.

(4) The desired product, guaifensin, gets crystallized upon cooling from the distillate collected in step (3).

The yield of the crude product 65.5 g having mp 77.5–78.5°C.

4.8.17.6 Precautions

(1) The condensation reaction between *o*-methoxyphenol and glycidol is quite exothermic in nature ; and hence the initial heating to 95°C should be done very carefully. Once the reaction gets started the application of external heating must be stopped completely. The heat generated by the reaction iteself should not be allowed to rise beyond 110°C at all.

(2) The distillation of the completed reaction mixture should be carried out at 0.55 Hg-pressure so as to collect the major portion of the distillate separately.

4.8.17.7 Recrystallization. The crude guaifensin is dissolved in ethanol (96% v/v) and the pure product is obtained as beautiful crystals, 63.5 g having mp 78–79.5°C.

4.8.17.8 Theoretical Yield/Practical Yield. The theoretical yield may be calculated from the equation under theory (section 4.8.17.3) as detailed below :

124 g of *o*-Methoxyphenol on condensation with Glycidol gives

rise to the formation of Guaifensin = 198.22 g

$\therefore$ 57 g of *o*-Methoxyphenol shall yield Guaifensin $= \frac{198.22}{124} \times 57 = 91.12$ g

$\therefore$ Theoretical Yield of Guaifensin = **91.12 g**

Reported Practical Yield = 65.5 g

Therefore, Percentage Practical Yield $= \frac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100$

$= \frac{65.5}{91.12} \times 100 =$ **71.88**

4.8.17.9 Physical Parameters. Guaifensin is obtained as minute rhombic prisms from ether, mp 78.5–79°C ; and bp_{19} 215°C. It has a slight bitter aromatic taste. 1 g dissolves in 20 ml water at 25°C ; much more soluble in hot water ; freely soluble in ethanol ; soluble in chloroform, glycerol, propylene glycol, DMF ; moderately soluble in benzene ; and almost insoluble in petroleum ether.

4.8.17.10 Uses

(1) It substantially reduces the viscosity of tenacious sputum and hence used as an expectorant in cough mixtures.

(2) A mixture with theophylline (1 : 1), known as *guaithylline*, is invariably employed as a bronchodilator.

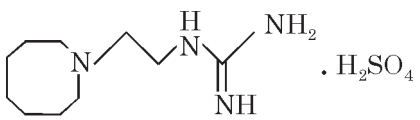
4.8.17.11 Questions for *Viva-Voce*

(1) How would you synthesize 'guaifensin' from *ortho*-methoxyphenol ? Explain.

(2) Why is it necessary to carry out the 'distillation' under vacuo ? Explain.

4.8.18 Guanethidine Sulphate

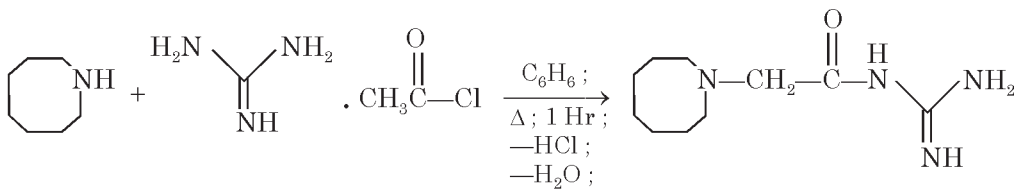
4.8.18.1 Chemical Structure



Guanethidine sulphate

4.8.18.2 Synonyms. [2-(Hexahydro-1(2H)-azocinyl)-ethyl] guanidine ; [2(Octahydro-1-azocinyl) ethyl] guanidine.

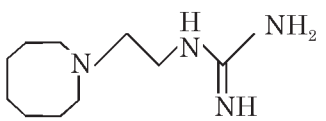
4.8.18.3 Theory



Heptamethylene imine (113)

Chloroacetyl guanide (137.5)

2-(1-N, N-Heptamethylene-imino)-acetic acid guanide



(*i*) $LiAlH_4$
(Reduction)
(*ii*) H_2SO_4

Guanethidine Sulphate (296.31)

Interaction between heptamethylene imine and chloroacetyl guanide in a medium of benzene yields 2-(1-N, N-heptamethylene imino)-acetic acid guanide with the elimination of a mole each of HCl and water. This particular intermediate on being subjected to reduction with lithium aluminium hydride [$LiAlH_4$] specifically converts the carbonyl function to methylene moiety with the elimination of a mole of water ; and finally producing the '*guanethidine base*', which upon treatment with a calculated amount of H_2SO_4 forms the corresponding salt *i.e.*, guanethidine sulphate.

4.8.18.4 Chemicals Required. Chloroacetyl guanide : 13.6 g ; Hepta-methylene imine : 22.6 g ; Benzene : 200 ml ; Tetrahydrofuran : 150 ml : Lithium aluminium hydride : 6 g ; Sodium hydroxide solution (2 M) : q.s. ; Sulphuric Acid (3 M) : q.s. ; Ethanol [96% (v/v)] : 150 ml.

4.8.18.5 Procedure. The various steps involved are as given below :

(1) 13.6 g (0.1 mol) Chloroacetyl guanide is added slowly with continuous stirring to a solution of 22.6 g (0.2 mol) hepta-methylene-imine in 200 ml benzene in a 500 ml beaker preferably on a magnetic stirrer-cum-hot plate. Warm the reaction mixture for 60 minutes and then cooled subsequently.

(2) The resulting solution is filtered and the filtrate concentrated under reduced pressure.

(3) The residue obtained from step (2), containing the 2-(1-N, N-heptamethylene-imino)-acetic acid guanide, an intermediate, is duly suspended in tetrahydrofuran ; and added to a previously refluxing solution of 6 g $LiAlH_4$ dissolved in tetrahydrofuran very slowly and carefully. Allow the refluxing to continue upto 30 minutes.

(4) After completion of the reaction, the excess of unreacted $LiAlH_4$ is suitably decomposed by the addition of water, followed by dilute aqueous NaOH solution. The solid material thus obtained is filtered off and rejected.

(5) The clear filtrate is acidified carefully with dilute sulphuric acid (3M) to litmus paper ; and the desired product *i.e.*, guanethidine sulphate may be obtained as crystals.

The yield of crude product is 44.85 g, mp 276–279°C.

4.8.18.6 Precautions

(1) Step-1 must be carried out on a magnetic-stirrer-cum-hot plate for at least 60 minutes to obtain the intermediate product *i.e.*, 2-(1-N, N-heptamethyleneimino)-acetic acid guanide.

(2) The intermediate product is dissolved duly in tetrahydrofuran and added to a solution of requisite amount of $LiAlH_4$ in tetrahydrofuran and not *vice-versa.*

(3) The unreacted $LiAlH_4$ must be decomposed in the reaction mixture as far as possible completely first by treatment with water, followed by aqueous NaOH solution.

4.8.18.7 Recrystallization. The crude product is usually recrystallized from aqueous ethanol to obtain beautiful crystals upto 42.9 g having mp 276–280°C (decomposes).

4.8.18.8 Theoretical Yield/Practical Yield. The theoretical yield is normally calculated from the equation stated under theory (section 4.8.18.3) as given under :

113 g of Heptamethylene imine on treatment with chloroacetyl guanide/ $LiAlH_4/H_2SO_4$ yield Guanethidine Sulphate = 296.31 g

$\therefore$ 22.6 g of Heptamethylene imine shall

yield Guanethidine Sulphate $= \frac{296.31}{113} \times 22.6 = 59.26$ g

Hence, Theoretical Yield of Guanethidine Sulphate = **59.26 g**

Reported Practical Yield = 44.85 g

Therefore, Percentage Practical Yield $= \frac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100$

$= \frac{44.85}{59.26} \times 100 =$ **75.68**

4.8.18.9 Physical Parameters. Guanethidine sulphate is obtained as crystals from dilute ethanol having mp 276–281°C (decomposes).

4.8.18.10 Uses

(1) It is an antihypertensive agent which acts by selectively inhibiting transmission in post ganglionic adrenergic nerves.

(2) It is used in the management of hypertension and in the topical treatment of *primary open angle glaucoma*.*

(3) It is also employed in the treatment of hypertension when other drugs proved inadequate.

(4) It is often administered with a diuretic or sometimes with antihypertensive agent.

4.8.18.11 Questions for *Viva-Voce*

(1) How does the intermediate 2-(1-N, N-heptamethylene imino)-acetic acid guanide upon reduction yields ***'Guanethidine Base'*** ? Explain.

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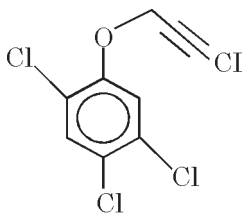
*It usually affects both eyes, and there is a characteristic change in the appearance of the optic disc.

(2) How do we usually prepare the corresponding acid salt from a base ? Explain with theoretical logistics.

4.8.19 Haloprogin

4.8.19.1 Chemical Structure

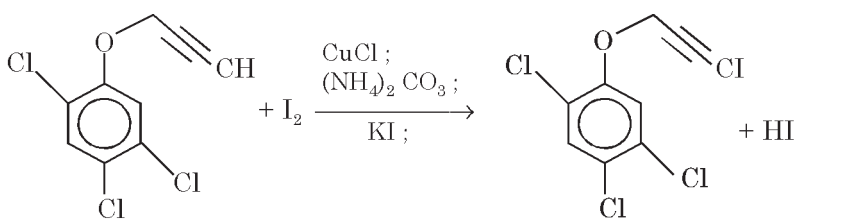


Haloprogin

4.8.19.2 Synonyms

3-Iodo-2-propynyl 2, 4, 5-trichlorophenyl ether ; 2, 4, 5-Trichlorophenyl γ-iodopropargyl ether.

4.8.19.3 Theory



2, 4, 5-Trichlorophenyl-propargyl ether (253.39)

Haloprogin (361.39)

Hydroiodic acid

The interaction between 2, 4, 5-trichlorophenyl propagyl ether and iodine, in the presence of cuprous chloride, ammonium carbonate to form cupro-ammonium complex salt, plus potassium iodide to solubilize iodine as its water-soluble complexes (as KI_2, KI_3, KI_4 .....) ultimately gives to the formation of haloprogin with the elimination of one mole of hydro-iodic acid.

4.8.19.4 Chemicals Required. 2, 4, 5-Trichlorophenyl propagyl ether : 4.7 g ; Cuprous chloride (CuCl) : 4 g ; Ammonium Carbonate : 11 g ; Iodine : 5 g ; Potassium Iodide : 5 g ; Ether : q.s. ; Hexane : q.s.

4.8.19.5 Procedure. The various steps undertaken in this synthesis are enumerated as given below :

(1) 4.7 g (0.02 mol) of 2, 4, 5-trichlorophenyl propagyl ether, having mp 64–65°C), is added to an aqueous solution of cupro-ammonium complex salt that has been prepared separately by warming carefully a mixture of 4 g cuprous chloride, 11 g ammonium carbonate and 20 ml water to 50°C.

(2) The resulting admixture is shaken vigorously. The cuprous acetylide deposited is filtered, washed with water and suspended in 100 ml of water ; and the suspension

thus obtained is mixed under agitation with a solution of 5 g iodine plus 5 g potassium iodide in 15 ml water. The mixture is stirred continuously and vigorously on a magnetic stirrer for a period of 1 hour.

(3) The precipitate is filtered in a Büchner funnel under suction, washed with a spray of water, and extracted successively with solvent ether.

(4) The combined ethereal extract is dried with anhydrous sodium sulphate ; and the solvent is distilled off over an electric water-bath.

The crude haloprogin 5.85 g with mp 113.5–115°C is obtained.

4.8.19.6 Precautions

(1) The solution of '*cupro-ammonium complex*' must be prepared afresh by warming the reactants carefully at 50°C.

(2) The reaction with iodine plus KI must be carried out under vigorous agitation at an ambient temperation for 60 minutes.

(3) Ether must be distilled off in a fuming cup-board (HIGHLY INFLAMMABLE).

4.8.19.7 Recrystallization. The crude product may be recrystallized from *n*-hexane to obtain as white or pale yellow crystals 5.6 g having mp 113–114°C.

4.8.19.8 Theoretical Yield/Practical Yield. The theoretical yield is calculated from the equation under theory (section 4.8.19.3) as stated below :

235.39 g Trichlorophenyl propagyl ether on iodination gives

rise to formation of Haloprogin = 361.39 g

∴ 4.7 g Trichlorophenyl propagyl ether shall yield Haloprogin

$$= \frac{361.39}{235.39} \times 4.7 = 7.22 \text{ g}$$

Hence, the Theoretical Yield of Haloprogin = **7.22 g**

Reported Practical Yield = 5.85 g

Therefore, Percentage Practical Yield

$$= \frac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100$$

$$= \frac{5.85}{7.22} \times 100 = \mathbf{81.02}$$

4.8.19.9 Physical Parameters. Haloprogin is obtained as white or pale yellow crystals, mp 113–114°C ; decomposes 190°C ; uv_{max} (anhydrous ethanol) : 288.5, 298.5 nm. It is found to be easily soluble in methanol, ethanol, very slightly soluble in water.

4.8.19.10 Uses

(1) It is used in the treatment of *dermatophytosis** and *pityriasis versicolor*.**

(2) It is usually applied topically as 1% (w/w) cream or lotion.

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*A fungus infection of the skin of the hands and feet, especially between the toes.

**General dermatitis caused due to *Tinea versicolor*.

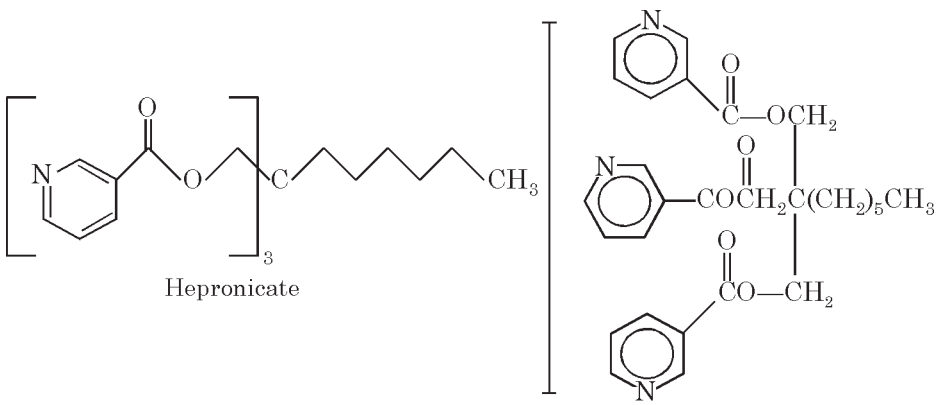
4.8.19.11 Questions for *Viva-Voce*

(1) How would you afford the '*iodination*' of Trichlorophenyl propagyl ether ? Explain.

(2) Why does it act as an '*antibacterial*' agent ?

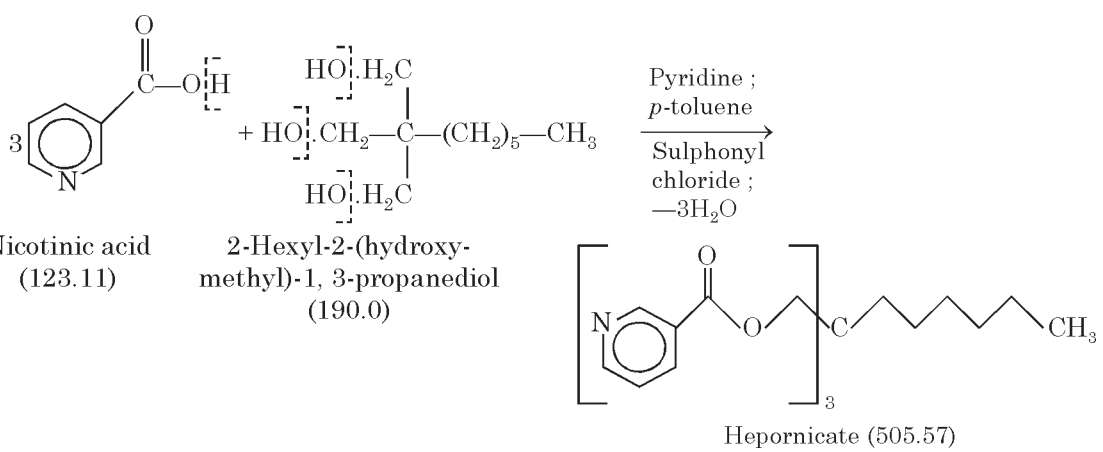
4.8.20. Hepronicate

4.8.20.1 Chemical Structure



4.8.20.2 Synonyms. 1, 1, 1-Trimethylolheptane trinicotinate; 1,1,1–(Trihydroxymethyl)-heptane trinicotinate ; 2-Hexyl-2-(hydromethyl)-1,3-propanediol trinicotinate ; 2,2-Dihydroxymethyl-*n*-octanol trinicotinate :

4.8.20.3 Theory



The interaction between 3 moles of nicotinic acid and 1 mole of 2-hexyl-2-(hydroxymethyl)-1,3-propanediol in the presence of pyridine as a medium and *para*-toluene sulphonyl chloride as a catalyst gives rise to the formation of 1 mole of the desired ester, hepornicate ; and 3 moles of water are eliminated.

4.8.20.4 Chemicals Required. Nicotinic Acid : 50 g ; Pyridine : 450 ml ; *p*-Toluene sulphonyl chloride : 50 g ; 2-Hexyl-2-(hydroxymethyl)-1,3-propanediol : 19 g ; Toluene : 200 ml ;

Aqueous sodium Bicarbonate [5% (w/v)] : q.s. ; Potassium carbonate : q.s. ; Ethanol [96% (v/v)] : 150 ml.

4.8.20.5 Procedure. The various steps involved are as given under :

(1) 50 g (0.4 mol) Nicotinic acid and 50 g (0.27 mol) *para*-toluene sulphonyl chloride were dissolved in 50 ml redistilled pyridine in a 1 L round bottom flask. While stirring, the mixture slowly became hot, due to the exothermic nature of the reaction mixture. It turned into a colourless product that finally solidified.

(2) To the resulting mixtrue was added dropwise a solution of 19 g (0.1 mol) 2-hexyl-2-(hydroxymethyl)-1, 3-propanediol in 400 ml redistilled pyridine at a temperature not exceeding 80°C in any case.

(3) The mixture was heated at 115°–125°C on a thermostatically controlled oil bath for a duration of 60 minutes. The contents of the flask were allowed to cool down to room temperature ; and subsequently poured into 300 ml of ice-cold water.

(4) The resulting product was extracted with toluene successively. The toluene-layer thus collected was washed in sequence with distilled water, aqueous sodium carbonate and finally with water. The resulting product was dried over anhydrous potassium carbonate, and subsequently the toluene was distilled off under vacuo.

(5) The oily residue was allowed to crystallize in ethanol to obtain the pure product 30 g mp ranging between 94°–96°C.

4.8.20.6 Precautions

(1) It is very important to note that the solution of 2-hexyl-2-(hydroxymethyl)-1,3-propanediol in pyridine must be added to the solution of nicotinic acid, *p*-toluene sulphonyl chloride in pyridine almost dropwise with frequent stirring (below 80°C).

(2) In organic synthesis it is very important to use ALWAYS FRESHLY DISTILLED PYRIDINE to obtain better yield and pure product.

(3) After extract with toluene, the combined toluene-layer must be washed strictly as per the aforesaid sequence.

4.8.20.7 Theoretical Yield/Practical Yield. The theoretical yield is calculated from the equation given under theory (section 4.8.20.3) as stated under :

369.33 g (= 123.11 × 3) Nicotinic Acid on being reacted with

2-Hexyl-2-(hydroxymethyl)-1, 3-propanediol yields

Hepornicate = 505.57 g

$\therefore$ 50 g Nicotinic Acid shall yield Hepornicate $= \frac{505.57}{369.33} \times 100 = 68.44$ g

Hence, Theoretical Yield of Hepornicate = **68.44 g**

Reported Practical Yield = 30 g

Therefore, Percentage Practical Yield $= \frac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100$

$= \frac{30}{68.44} \times 100 =$ **43.83**

4.8.20.8 Physical Parameters. The crystals of hepornicate from ethanol has a mp 94–96°C.

4.8.20.9 Uses. It is a vasodilator used in the treatment of peripheral disorders.

4.8.20.10 Questions for *Viva-Voce*

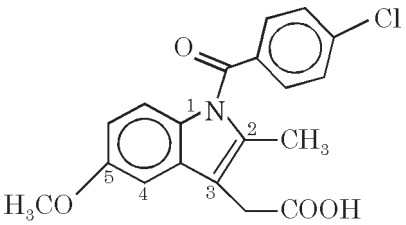
(1) How would you synthesize a '*peripheral vasodilator*' from nicotinic acid ?

(2) Why do we use *para*-toluene sulphonyl chloride in this synthesis ? Explain.

(3) Why is it necessary and important to use freshly redistilled pyridine in the synthesis of 'medicinal compounds' ? Explain.

4.8.21 Indomethacin

4.8.21.1 Chemical Structure

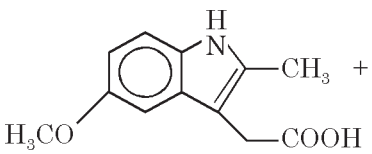


Indomethacin

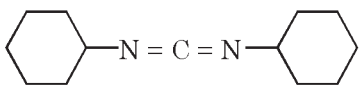
4.8.21.2 Synonyms. 1-(p-Chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetic acid ; 1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid ;

4.8.21.3 Theory

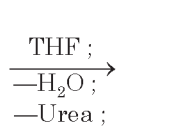
(*a*)

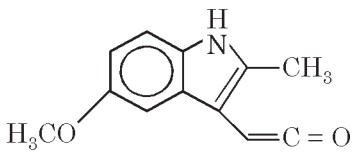


2-Methyl-5-methoxy-3-indole acetic acid (207)



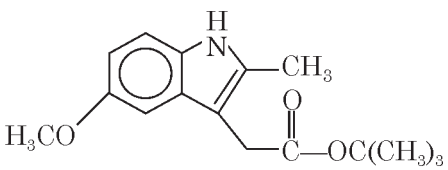
Dicyclohexyl-carbodiimide (206.33)



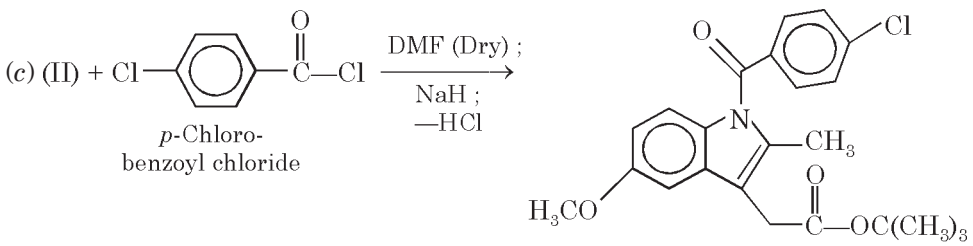


2-Methyl-5-methoxy-3-indolylacetic anhydride (OILY) (I)

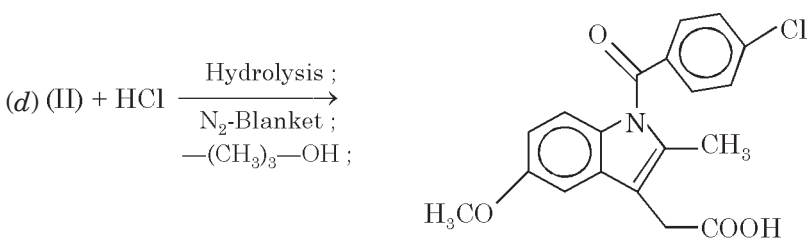
(*b*) (I) + $(CH_3)_3COH$ (*tert*-Butanol) $\xrightarrow[\text{EtOH ; Refluxed (16 HRS.)}]{ZnCl_2 \text{ (fused)}}$



t-Butyl-2-methyl-5-methoxy-3-indolyl acetate (II) [OILY ESTER]



tert-Butyl-1-*p*-chlorobenzoyl-
2-methyl-5-methoxy-3-indolyl-acetate
(III)



Indomethacin
(357.79)

In Eqn. (*a*) : dichlorohexylcarbodiimide undergoes an interaction with 2-methyl-5-methoxy-3-indole acetic acid in the presence of tetrahydrofuran (THF) when 2-methyl-5-methoxy-3-indolylacetic anhydride (I) is obtained with the elimination of a mole of urea.

In Eqn. (*b*) : compound (I) is made to reflux with *tert*-butanol in the presence of fused $ZnCl_2$ for 16 hours at a stretch when the corresponding ester *tert*-butyl-2-methyl-5-methoxy-3-indolyl acetate (II) is obtained.

In Eqn. (*c*) : compound (II) is treated with *p*-chloro-benzoyl chloride in the presence of dry dimethyl formamide and sodium hydride when the corresponding *n*-substituted ester *i.e.*, *tert*-butyl-1-*p*-chlorobenzoyl-2-methyl-5-methoxy-3-indolyl-acetate (III) is formed with the elimination of one mole of HCl.

Finally, in Eqn. (*d*) the resulting product (III) is subjected to hydrolysis in an acidic medium under a blanket of N_2, when the desired product indomethacin is obtained with the elimination of *tert*-butanol.

4.8.21.4 Chemicals Required. Dicyclohexylcarbodiimide : 10 g ; 2-Methyl-5-methoxy-3-indolylacetic acid : 22 g ; Tetrahydrofuran (THF) : 200 ml ; Skellysolve B : q.s. ; *t*-Butyl alcohol : 25 ml ; Zinc chloride (fused) : 0.3 g ; Ether : q.s. ; Saturated Sodium Bicarbonate (aqueous) : q.s. ; Aqueous saturated salt solution : q.s. ; Dry Dimethylformamide (DMF) : 450 ml ; Sodium hydride (50% susp.) : 4.9 g ; *para*-Chlorobenzoyl chloride : 15 g ; Acetic acid [5% (v/v)] : 1 L ; Benzene : q.s. ; Anhydrous Magnesium Sulphate : q.s. ; Activated charcoal powder : q.s. ; Methanol q.s. ; Powdered Porous plate : 1 g ; Acetic Acid : q.s. ; Dilute HCl (2 M) : q.s. ; Aqueous Ethanol : q.s.

4.8.21.5 Procedure. The different steps adopted in the synthesis of indomethacin are enumerated below sequentially :

Step I. Preparation of 2-Methyl-5-methoxy-3-indolylacetic anhydrides :

(1) Dissolve 10 g (0.49 mol) dicyclohexylcarbodiimide in a solution of 2-methyl-5-methoxy-3-indolyl acetic acid (22 g ; 0.10 mol) in 200 ml of tetrahydro furan (THF) ; and the solution is maintained at room temperature 25 ± 2°C for at least 2 hours.

(2) The precipitated urea is removed in a Büchner funnel under suction ; and the resulting filtrate is evaporated in vacuo to a small residue and subsequently flushed with Skellysolve B.

(3) The residual oily anhydride (I) is used without any purification in the next step.

Step-II. Preparation of *tert*-Butyl-2-methyl-5-methoxy-3-indolylacetate :

(1) The whole of the anhydride obtained from Step-I, is added carefully to 25 ml *tert*-butyl alcohol and 0.3 g fused zinc chloride. The resulting solution is refluxed for 16 hours at a stretch ; and the excess of unreacted *t*-butyl alcohol is removed under reduced pressure.

(2) The residue, thus obtained, is dissolved in ether, washed several times with saturated bicarbonate, water and saturated salt solution.

(3) After drying over anhydrous $MgSO_4$, the resulting solution is treated with charcoal, evaporated, and flushed several times with Skellysove B for complete removal of alcohol.

(4) The residual oily ester (18 g ; 93%) is used without any purification whatsoever in Step-III.

Step-III. Preparation of *tert*-Butyl-1-*p*-chlorobenzoyl-2-methyl-5-methoxy-3-indolylacetate :

(1) A stirred solution of ester (II) (18 g ; 0.065 mol) in dry dimethylformamide (DMF) (450 ml) is eventually cooled down to 4°C in an ice-bath, and sodium hydride (4.9 g, 0.098 mol, 50% suspension) is added in small lots at intervals.

(2) After a duration of 15–20 minutes, 15 g (0.085 mol) *para*-chlorobenzoyl chloride is added dropwise over a span of 10–15 minutes, and the mixture is stirred for 9 hours continuously *without replenishing the ice-bath.*

(3) The resulting mixture is then poured into 1 L to 5% (v/v) acetic acid, extracted successively with a mixture of ether and benzene, washed thoroughly with water, bicarbonate, saturated salt, dried over $MgSO_4$, treated with charcoal, and evaporated to a residue that partly crystallizes.

(4) The residue is shaken with ether, filtered and the filtrate is carefully evaporated to a residue (17 g) that solidifies after being refregerated overnight.

(5) The entire crude product is boiled gently with 300 ml Skellysolve B, cooled to room temperature, decanted from certain '*gummy material*', treated with activated charcoal, concentrated to 100 ml, and allowed to crystallize. The product, thus obtained (10 g) is recrystallized from 50 ml of methanol ; and yields 4.5 g of analytically pure material having mp 103–104°C.

Step IV. 1-*para*-Chlorobenzoyl-2-methyl-5-methoxy-3-indolylacetic acid :

(1) A mixture of 4.5 g ester (III) and 0.45 g powdered porous plate is heated in an oil-bath maintained at 210°C, with continuous magnetic stirring, under a blanket of N_2 for a duration of 2 hours. **No intensification of colour** (*pale yellow*) **takes place during this period.**

(2) The resulting product is cooled under N_2, dissolved in benzene and ether, filtered, and extracted with bicarbonate.

(3) The aqueous solution is filtered with suction to get rid of ether, neutralized with acetic acid carefully, and then acidified weakly with dilute HCl.

(4) The yield of the crude product is 2.2 g having mp ranging between 149–150.5°C.

4.8.21.6 Precautions

(1) It is a multi-step synthesis ; and, therefore, each step (I through IV) has to be followed rigidly and meticulously.

(2) All reagents must be of maximum purity so as to achieve pure product at each step ; and, hence, the final product should also be in the purest form.

4.8.21.7 Recrystallization. The entire curde product (2.2 g) is recrystallized from aqueous ethanol and subsequently dried under vacuo at a temperature not exceeding 65°C.

The yield of the pure product is 2.0 g having mp 151°C.

4.8.21.8 Physical Parameters. The crystals of indomethacin usually exhibits **polymorphism*** having mp for one form ~ 155°C and the other ~ 162°C. It has uv_{max} (ethanol) : 230, 260, 319 nm ($\in$ 20800, 16200, 6290) ; pKa 4.5. It is found to be soluble in ethanol, acetone, caster oil ; almost insoluble in water. It is quite stable in neutral or slightly acidic media, and found to be decomposed by strong alkali.

4.8.21.9 Uses

(1) It is a potent non-steroidal anti-inflammatory drug (NSAID).

(2) It is used in musculoskeletal and joint disorders including ankylosing spondylitis, osteoarthritis, rheumatoid arthritis and acute gouty arthritis.

(3) It is employed in peri-articular disorders *e.g.,* bursitis**, and tendinitis.

(4) It is also used in pain, inflammation and oedema orthopaedic procedures.

(5) It is used in mild to moderate pain in dysmenorrhoea.

(6) It is employed as an adjunct to opioids in the control and management of post-operative pain.

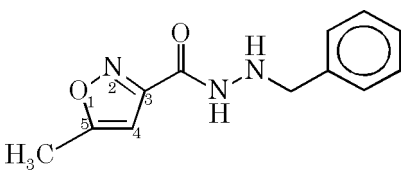
4.8.21.10 Questions for Viva-Voce

(1) What are the four distinct steps involved in the synthesis of '*Indomethacin*' ? Explain.

(2) How would you explain the elimination of '*urea*' in the very first step of the synthesis of indomethacin ?

4.8.22 Isocarboxazid

4.8.22.1 Chemical Structure



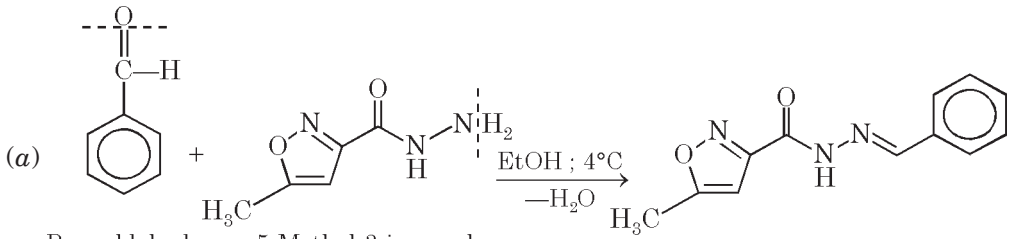
Isocarboxazid

*Polymorphism. The property of crystallizing in two or more different forms.

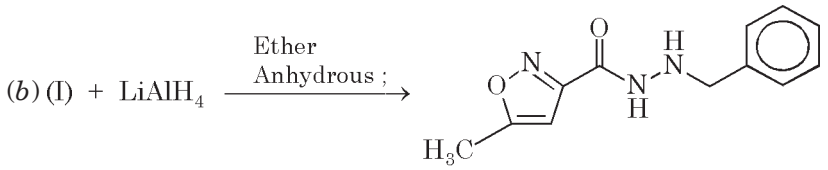
**Bursitis. Inflammation of a bursa (*i.e.,* a pad-like sac or cavity found in connective tissue) those located between bony prominences and muscle or tendon.

4.8.22.2 Synonyms. 3-(N-Benzylhydrazinocarbonyl)-5-methyl-isoxazole ; 1-Benzyl-2-(5-methyl-3-isoxazolylcarbonyl) hydrazine ;

4.8.22.3 Theory



Benzaldehyde (106) | 5-Methyl-3-isoxazole-carboxylic acid hydrazide (141.35) | 1-Benzylidene-2-(5-methyl-3-isoxazolylcarbonyl) hydrazine (229.35) (I)



Isocarboxazid (229.35)

The synthesis of isocarboxazid may be accomplished in **two** parts, namely :

Eqn. (*a*) : shows the interaction between benzaldehyde and 5-methyl-3-isoxazole carboxylic acid hydrazide in the presence of ethanol at 4°C to yield 1-benzylidene-2 (5-methyl-3-isoxazolylcarbonyl) hydrazine (I) with the elimination of one mole of water as indicated above.

Eqn. (*b*) : illustrates evidently the reduction of (I) obtained from the previous step with pure Lithium Aluminium Hydride ($LiAlH_4$) in a medium of anhydrous ether to form the desired compound, isocarboxazid, with the addition of 2H-atoms to the N = C in (I).

4.8.22.4 Chemicals Required. Benzaldehyde : 80 g ; Ethanol [95% (v/v)] : 750 ml ; 5-Methyl-3-isoxazole-carboxylic acid hydrazide : 72 g ; 1-Benzylidene-2-(5-methyl-3-isoxazolylcarbonyl) hydrazine : 11.5 g ; Anhydrous Solvent Ether : 500 ml ; Pure $LiAlH_4$: 1.85 g ; Ethyl acetate : 25 ml ; Benzene : 20 ml ; Methanol : q.s.

4.8.22.5 Procedure. The various steps involved in the synthesis are enumerated below in a sequential manner :

(1) 80 g (0.75 ml) Benzaldehyde (freshly distilled, bp 179°C) was added to a hot solution (75°C) of 700 ml ethanol containing 72 g (0.5 mol) 5-methyl-3-isoxazole carboxylic acid hydrazide. The resulting solution was stirred for 10-15 minutes at which time the **'intermediate product'** started to crystallize.

(2) The reaction mixture was allowed to cool at 4°C for a duration of 14 hours ; the resulting solid was filtered off under vacuum and the solid filter cake was washed twice using 25 ml of ice-cold ethanol for each washing. The **'intermediate product'** 1-benzylidene-2-(5-methyl-3-isoxazolycarbonyl) hydrazine (I) was recrystallized from ethanol, mp 199–200°C.

(3) 11.5 g (0.05 mol) of (I) was added in small lot at intervals, over a duration of 60–70 minutes, into 500 ml of anhydrous solvent ether containing 1.85 g lithium aluminium

hydride. The reaction mixture was stirred mechanically at a stretch for 4 hours ; and then allowed to stand overnight.

(4) The excess of $LiAlH_4$ (unreacted) was decomposed with 25 ml ethyl acetate and 15 ml water was further added to decompose the **'complex'** formed. The solid residue thus obtained was separated by filteration and the ethereal layer was concentrated to about 50 ml.

(5) 20 ml dry benzene was added to the resulting concentrated ethereal layer in order to dehydrate the latter. The concentration was further continued carefully until a solid residue remained. The crude product was recrystallized from minimum quantity of methanol to obtain crystals of pure **isocarboxazid** 83.5 g having mp 105–106°C.

4.8.22.6 Precautions

(1) The *'intermediate product'* (I) is a heat-sensitive one, and, therefore, must be chilled to 4°C for about 14 hours to recover it. It must be recrystallized from ethanol at this stang only so as to obtain a better yield and relatively pure product in the final stage.

(2) The excess of unreacted $LiAlH_4$ should be decomposed and removed from the reaction mixture as a filterable solid residue.

(3) The final ethereal concentrated layer is essentially required to be dehydrated first with benzene (dry) and the crude product to be recrystallized from methanol.

4.8.22.7 Physical Parameters. It is normally obtained as a practically tasteless crystals obtained from methanol, mp 105–106°C. It is found to be very sparingly soluble in hot water (0.05%), somewhat more (1 to 2%) in [95% (v/v)] ethanol ; and also soluble in glycerol and in propylene glycol.

4.8.22.8 Uses

(1) It is employed in the treatment of depression but the obvious risks associated with irreversible MAOIs usually mean that other depressants are most preferred.

(2) It is found to be an irreversible inhibitor of both monoamine oxidase types A and B.

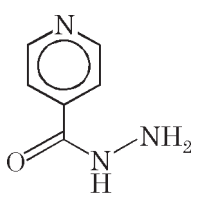
4.8.22.9 Questions for *Viva-Voce*

(1) How would you explain the mechanism of reaction to form 1-benzylidene-2-(5-methyl-3-isoxazolylcarbonyl)-hydrazine ?

(2) Why is it necessary to decompose the excess of the unreacted $LiAlH_4$ from the reaction mixture before proceeding to the final recovery of the desired product *i.e.,* **isocarboxazid** ?

4.8.23 Isoniazid

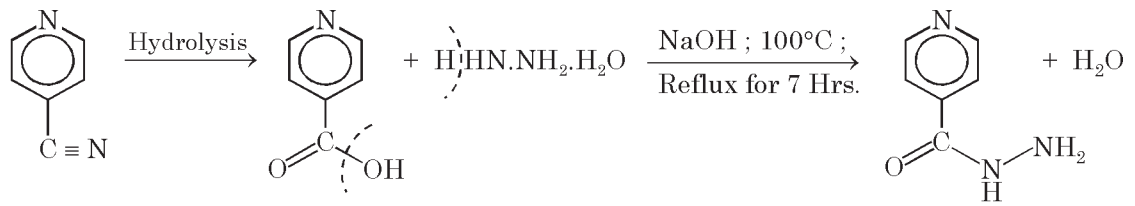
4.8.23.1 Chemical Structure



Isoniazid

4.8.23.2 Synonyms. 4-Pyridinecarboxylic acid hydrazide ; Isonicotinic acid hydrazide ; Isonicotinoylhydrazine ; Isonicotinylhydrazine ; INH.

4.8.23.3 Theory



First of all the 4-cyanopyridine undergoes hydrolysis whereby the cyano function at the C-4 position gets converted to a carboxylic moiety to form 4-pyridine carboxylic acid. Now, this resulting product on being treated with hydrazine hydrate, in the presence of NaOH and subjected to vigorous reflux for a long duration, gives rise to the formation of *isoniazid* with the elimination of a mole of water as indicated above.

4.8.23.4 Chemicals Required. 4-Cyanopyridine : 20.8 g ; Hydrazine Hydrate : 10 g ; Sodium Hydroxide : 0.016 g ; Ethanol [96% (v/v)] : q.s. ;

4.8.23.5 Procedure. The various steps adopted for the synthesis of isoniazid are as follows :

(1) 20.8 g (0.2 mol) 4-cyanopyridine in 125 ml water were reacted with 10 g (0.2 mol) hydrazine hydrate in the presence of 0.016 g (0.04 mol) sodium hydroxide at 100°C under reflux on a heating mantle for a duration of 7–8 hours at a stretch.

(2) The resulting mixture was filtered in Büchner funnel under suction and the clear filtrate was evaporated to dryness on an electric water-bath carefully.

(3) The yield of the crudue product was 17 g, mp 170–171°C.

4.8.23.6 Precautions

(1) The first step of the synthesis is extremely critical and hence important ; and, therefore, the gentle reflux at 100°C is to be carried out for 7–8 hours continuously.

(2) The evaporation of the filtrate is to be done over an electric water-bath carefully.

4.8.23.7 Recrystallization

The crude product is recrystallized from minimum quantity of ethanol to obtain crystals of the pure product having an yield of 15.6 g, mp 171.4°C.

4.8.23.8 Theoretical Yield/Practical Yield. The theoretical yield is calculated from the equation under theory (section 4.8.23.3) as stated under :

104 g 4-Cyanopyridine on being reacted with Hydrazine Hydrate

yields Isoniazid = 137.14 g

$$\therefore \quad 20.8 \text{ g 4-Cyanopyridine shall yield Isoniazid} = \frac{137.14}{104} \times 20.8 = 27.42 \text{ g}$$

Hence, Theoretical Yield of Isoniazid = **27.42 g**

Reported Practical Yield = 17 g

Therefore, Percentage Practical Yield $= \frac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100$

$= \frac{17}{27.42} \times 100 =$ **61.99**

4.8.23.9 Physical Parameters. Isoniazid is obtained as crystals from ethanol, mp 171.4°. It has uv_{max} (water) : 266 nm ($E^{1\%}_{1\,cm}$ 378) ; (0.01 N HCl) : 265 nm ($E^{1\%}_{1\,cm}$ ~ 420) . It is found to be soluble in water at 25°C : about 14% ; at 40°C : about 26% ; in ethanol at 25°C : about 2% ; in boiling ethanol : about 10% ; in chloroform : about 0.1%. It is almost insoluble in ether and benzene. The pH of a 1% (w/v) aqueous solution is 5.5 to 6.5. The aqueous solution may be sterilized at 120°C for 30 minutes.

4.8.23.10 Uses

(1) Being a hydrazid derivative it is the main stay of primary treatment of pulmonary and extrapulmonary tuberculosis.

(2) It is usually administered with other antituberculous agents *e.g.,* rifampicin and pyrazinamide.

(3) It is also used in high-risk subjects for the prophylaxis of tuberculosis (TB).

(4) It has also been given in regimens for the treatment of opportunistic mycobacterial infections.

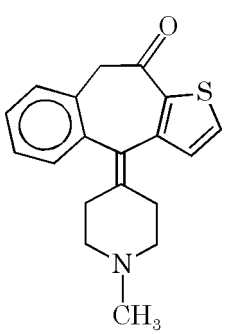
4.8.23.11 Questions for *Viva-Voce*

(1) What is the mechanism of the synthesis of **'isoniazid'** from 4-cyanopyridine ?

(2) What is the role of trace amount of NaOH in this reaction ?

4.8.24 Ketotifen

4.8.24.1 Chemical Structure

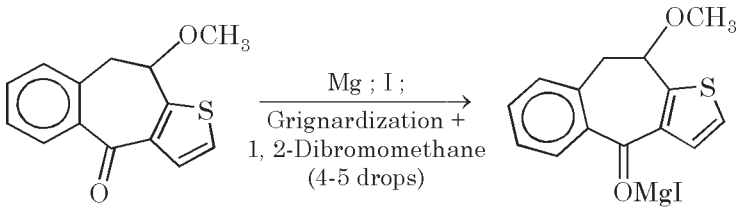


Ketotifen

4.8.24.2 Synonyms. 4, 9-Dihydro-4-(1-methyl-4-piperidinylidene)-10H-benzo [4, 5] cyclohepta [1, 2-*b*] thiophen-10-one ; 4-(1-Methyl-4-piperidylidene)-4H-benzo [4, 5] cyclohepta [1, 2-*b*]-thiophen-10 (9H)-one.

4.8.24.3 Theory

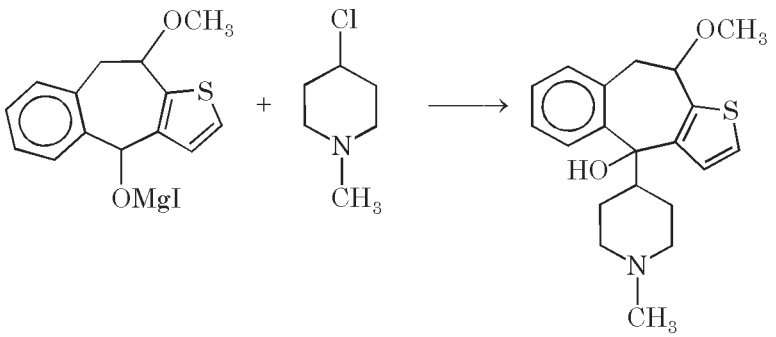
(*a*)



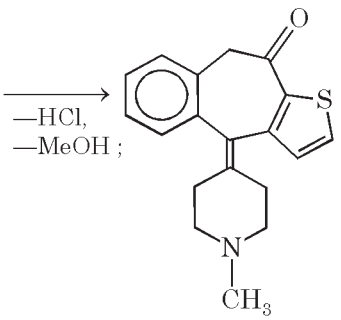
10-Methoxy-4H-benzo [4, 5] cyclohepta [1, 2-*b*] thiophen-4-one (I)

Grignard's derivative (II)

(*b*)



(II) 4-Chloro-1-methyl-piperidine (133.5) 10-Methoxy-4-(1-methyl-4-piperidyl)-4H-benzo [4, 5] cycloheptal [1, 2-*b*]-thiophen-4-ol [BASE] (III) (341)



Ketotifen (309.43)

Equation (*a*) depicts the Grignardization of 10-methoxy-4 H-benzo [4, 5] cyclohepta [1, 2-*b*] thiophen-4-one (I) with iodine-activated magnesium shavings in a medium of tetrahydrofuran to give rise to the formation of the corresponding Grignard's derivative (II).

Equation (*b*) shows the interaction of (II) with 4-chloro-1-methylpiperidine to form the *intermediate* 10-methoxy-4- (1-methyl-4-piperidyl)-4 H-benzo [4, 5] cycloheptal [1, 2-*b*]-thiophen-4-ol (III). The resulting intermediate (III) finally forms **ketotifen** with the elimination of one mole each of hydrochloric acid and methanol.

4.8.24.4 Chemicals Required. 4-Chloro-1-methylpiperidine : 17.7 g ; Iodine-activated Magnesium : 3.07 g ; Tetrahydrofuran (THF) : 100 ml ; 1, 2-Dibromomethane : 4-5 drops ; 10-Methoxy-4H-benzo [4, 5]-cyclohepta [1, 2-*b*] thiophen-4-ol : 15.3 g ; Ammonium chloride :

20 g ; Chloroform : q.s. ; 10-Methoxy-4-(1-methyl-4-piperidyl)-4H-benzo [4, 5] cycloheptal [1, 2-*b*] thiophen-4-ol [Base] : 3.4 g ; Sodium hydroxide solution [10% (w/v)] : 50 ml ; Ethanol [95% (w/v)] : q.s. ; Absolute ethanol : 270 ml ; HCl (3 M) : 40 ml ;

4.8.24.5 Procedure. The various steps involved in the synthesis are enumerated below :

(1) 3.07 g iodine-activated magnesium shavings are duly covered with a layer of 25 ml tetrahydrofuran, and approximately 1/10th of a solution of 17.7 g (0.132 mol) 4-chloro-1-methyl piperidine (base) in 70 ml absolute THF.

(2) The *Grignard Reaction* is initiated by the addition of a few drops of 1,2-dibromomethane. Now, the remaining 4-chloro-1-methylpiperidine solution is added dropwise to the magnesium at such a rate that the reaction mixture just boils continuously at reflux **without any external heating.** Boiling at reflux is then continued for 60 minutes. 15.3 g (0.0625 mol) 10-methoxy-4H-benzo [4, 5] cyclohepta [1, 2-*b*] thiopehn-4-one are added subsequently in small lots at intervals at 20°C, within 40 minutes, with slight external cooling. After stirring for 90-100 minutes, the reaction solution is poured on a mixture of 180 g ice and 20 g ammonium chloride. The **'free-base'** is successively extracted with chloroform (50 ml each time).

(3) The combined chloroform solution is concentrated under vacuo ; and the residue recrystallized from 270 ml absolute ethanol to obtain almost pure 10-methoxy-4-(1-methyl-4-piperidyl)-4H-benzo [4, 5] cyclohepta [1, 2-*b*]-thiopehn-4-ol (base, (III) having mp ranging between 194-196°C ; (molecular formula $C_{20}H_{23}NO_2S$).

(4) A mixture of 3.4 g (0.01 mol) of III (base) and 40 ml HCl (3 M) is kept in a boiling electric water-both at 95°–100°C for 60 minutes. The resulting mixture is rendered alkaline with sodium hydroxide solution (10% w/v) carefully at 20°C while cooling ; and the **free-base** thus liberated is extracted with chloroform successively. The combined chloroform extract is subsequently concentrated, preferably under reduced pressure, and the residue is recrystallized from ethanol : water (1 : 1).

The pure ketotifen is obtained to the extent of 26.6 g having mp 152–153°C.

4.8.24.6 Precautions

(1) Grignardization of compound (I) with iodine-activated magnesium shavings plus a few drops of 1, 2-dibromo-methane must be carried out very carefully to obtain the corresponding derivative (II).

(2) The interaction of derivative (II) with 4-chloro-1-methyl-piperidine to obtain the corresponding base (III) should be carried out with utmost precautions.

(3) The removal of chloroform must be carried out under vacuo preferably to avoid any possible deterioration of the desired product, ketotifen.

4.8.24.7 Theoretical Yield/Practical Yield. The theoretical yield is normally calculated from the equations (*a*) and (*b*) given under theory (section 4.8.24.3) as stated under :

133.5 g 4-Chloro-1-methylpiperidine on interaction with 10-methoxy-4H-benzo [4, 5] cyclohepta [1, 2-*b*] thiophen-4-one

yields Ketotifen = 309.43 g

∴ 17.7 g 4-Chloro-1-methylpiperidine shall

yield Ketotifen $= \frac{309.43}{133.5} \times 17.7 = 41.02$ g

Hence, Theoretical Yield of Ketotifen = **41.02 g**

Reported Practical Yield = 26.6 g

Therefore, Percentage Practical Yield $= \frac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100$

$= \frac{26.6}{41.02} \times 100 =$ **64.85**

4.8.24.8 Physical Parameters. The crystals of Ketotifen obtained from ethyl acetate has a mp ranging between 152–153°C.

4.8.24.9 Uses

(1) It has the properties of the antihistamines, in addition to a stabilizing action on mast cells analogous to that of sodium cromoglycate.

(2) It is administered orally in the prophylactic management of asthma.

(3) It is also used in the treatment of allergic conditions *e.g., rhinitis* and *conjunctivitis.*

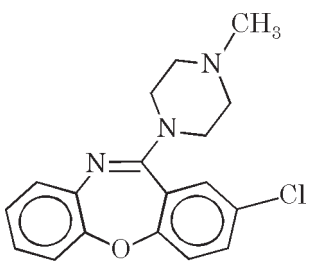
4.8.24.10 Questions for *Viva-Voce*

(1) Why is it necessary to Grignardize compound (I) before interacting with 4-chloro-1-methylpiperidine to obtain the base (III) *via* derivative (II) ?

(2) **Ketotifen fumarate** is the salt which finds its common usage as a '*drug*' rather than the *Ketotifen base.* Explain.

4.8.25 Loxapine

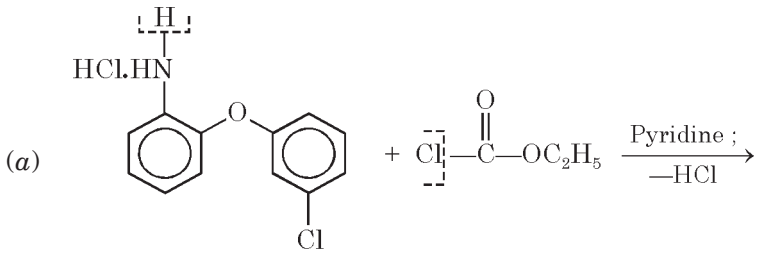
4.8.25.1 Chemical Structure



Loxapine

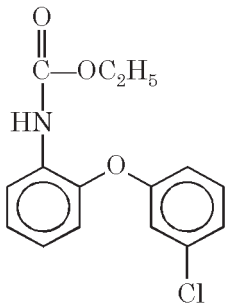
4.8.25.2 Synonyms. 2-Chloro-11-(4-methyl-1-piperazinyl) dibenz [*b*, *f*] [1, 4] oxazepine ; Oxilapine.

4.8.25.3 Theory. The synthesis of loxapine takes place under *three* different steps (*a*) through (*c*) as indicate under having specific reaction conditions and reagents :

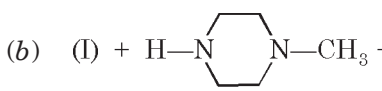


o-(*p*-Chlorophenoxy) aniline hydrochloride [Salt : 256, Base : 219.5]

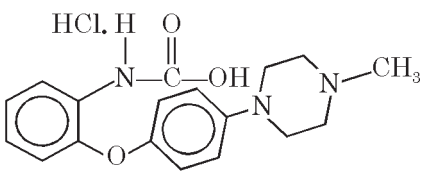
Ethyl chloroformate (108.52)



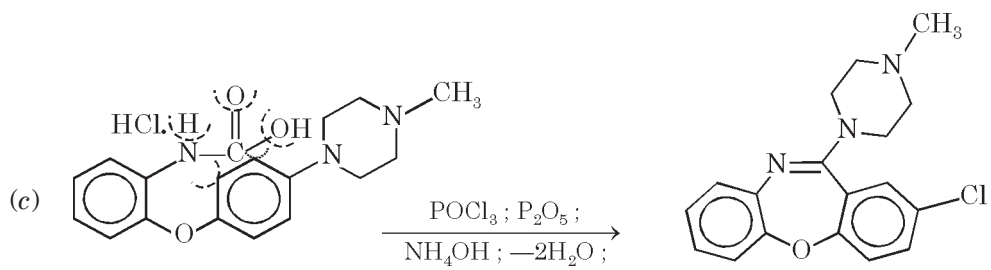
Ethyl-*o*-(*p*-chlorophenoxy)-carbanilate (I)



1-Methylpiperazine



4-Methyl-2′-(*p*-chlorophenoxy) 1-piperazine carboxanilide hydrochloride (II)



(III)

Loxapine (III) (327.81)

Equation (*a*) shows the interaction of the *o*-(*para*-chlorophenoxy) aniline hydrochloride (*i.e.,* salt) with ethyl chloroformate in the presence of pyridine to produce ethyl-*o*-(*p*-chlorophenoxy) carbanilate (I) with the elimination of one mole of HCl.

Equation (*b*) illustrates the reaction of (I) with 1-methylpiperazine, in the presence of benzene, sodium methoxide, to yield the intermediate compound (II) *i.e.,* 4-methyl-2′-(*p*-chlorophenoxy)-1-piperazine carboxanilide hydrochloride ; and one mole each of HCl and EtOH are eliminated.

Equation (*c*) depicts intramolecular rearrangement of (II) causing cyclization to form the **'oxazepine'** ring in the presence of $POCl_3/P_2O_5$ and concentrated ammonia solution to give rise to the formation of the desired compound, **loxapine**, with the elimination of two moles of water.

4.8.25.4 Chemicals required. *o*-(*para*-Chlorophenoxy) aniline base : 32 g ; Hydrochloric acid (12 M) ; q.s. ; Pyridine : 50 ml ; Ethyl chloroformate : 25 ml ; Ether : 1L ; Anhydrous sodium sulphate : q.s. ; Benzene : 20 ml ; 1-Methylpiperazine : 20 ml ; Sodium methoxide : 50 mg ; Petroleum ether : q.s. ; Chloroform : 200 ml ; Anhydrous HCl-gas : q.s. ; Phosphorous oxychloride : 50 ml ; Phosphorous pentoxide : 10 g ; Ammonium Hydroxide (conc.) : q.s. ; KOH pellets : q.s. ; Dilute hydrochloric acid (6M) : q.s.

4.8.25.2 Procedure. The various steps involved in the synthesis to *'loxapine'* are as stated below :

(1) To a mixture of *o*-(*para*-chlorophenoxy) aniline hydrochloride [prepared from 32 g (0.15 mol) of the base] in 50 ml redistilled pyridine is added very gradually while heating under reflux to 25 ml (21.7 g ; 0.2 mol) ethyl chloroformate). Once the addition is completed duly, the resulting mixture is then heated under reflux for 60–70 minutes further ; and subsequently evaporated under reduced pressure to an **oily residue.**

(2) The 'oily residue' thus obtained is taken up in 300 ml water, and extracted successively with ether (approximately 200 ml). The combined ethereal extract is dried over sodium sulphate (anhydrous) ; and evaporated to an oily residue (40 g) which contains ethyl, *o*-(*para*-chlorophenoxy) carbanilate (I) that may be used as such (without any purification) in the next step of the synthesis.

(3) The crude product (I) is dissolved in 20 ml benzene, and 20 ml (0.2 mol) 1-methylpiperazine and a small amount of sodium methoxide (freshly prepared ; upto 25–50 mg) are added. Benzene is removed by *'slow distillation'* ; and the resulting mixture is heated overnight under reflux (approx. 16 hours at a stretch).

(4) Evaporation of the above mixture under vacuo then leaves behind a solid residue that is made to dissolve in 400 ml of ether with warming in a water-bath. Concentration to almost half the original volume strictly under vacuo gives rise to a definite precipitate which is collected, washed with petroleum ether and dried in a dessiccator (36 g).

(5) A second crop is a also collected from the ensuing filtrate. This product is dissolved in 200 ml chloroform and treated with an excess of anhydrous hydrogen chloride (gas). The precipitate thus obtained is collected and dried at 50°C (in vacuo). It is the penultimate intermediate called 4-methyl-2′-(*para*-chlorophenoxy-1-piperazine carboxanilide hydrochloride (II) having mp 210–213°C.

(6) A mixture of 6 g (II), 50 ml $POCl_3$, and 10 g P_2O_5 is heated carefully under reflux for about 24 hours, and subsequently concentrated to a *gummy residue* by evaporation

under reduced pressure. The gummy residue is taken up in 150 ml ether, 200 g crushed ice is added, and the mixture is made alkaline with conc. NH_4OH (cautiously). The ethereal layer is separated with the help of a separating funnel, dried over KOH pellets and evaporated to a solid residue (approximately 4 g).

(7) The crude product (4 g) is dissolved in nearly 100 ml dilute HCl (6 M), the acidic solution is extracted with ether, and the aqueous layer is made alkaline with (3 M) NaOH solution in the presence of ether (approximately 250 ml). The ethereal layer is separated, dried over KOH pellets, and evaporated in a fuming cup-board to a white solid.

(8) **Further purification** may be carried out by repeating the formation of the HCl-salt, and reprecipitation of the base. When purified in this fashion, followed by drying at 80°C in vacuo over P_2O_5, the final desired product (III), *loxapine* is obtained having mp ranging between 109–111°C.

4.8.25.6 Precautions

(1) All reagents used in various steps involved in the synthesis of **'loxapine'** should be of highest purity, freshly distilled, freshly prepared so as to obtain the maximum yield and purest end products.

(2) The final step of the synthesis involving the **'cyclization'** of oxazepine ring is extremely important and critical. Hence, every fine details of each steps stated above must be followed rigidly.

4.8.25.7. Physical Parameters. It is obtained as pale-yellow crystals from petroleum ether having mp ranging between 109–110°C.

4.8.25.8 Uses

(1) It is indicated in the treatment of *psychoses.*

(2) It is invariably employed in the control and management of psychoses ; and also as an antipsychotic in *schizophrenia*.

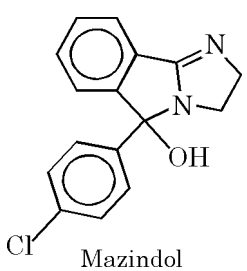
4.8.25.9 Questions for *Viva-Voce*

(1) How would you accomplish the synthesis of *'Loxapine'* starting from *o*-(*para*-Chlorophenoxy) aniline ? Explain.

(2) What are the **three** products/intermediates in this synthesis that were dried over *'anhydrous sodium sulphate'*, *'potassium hydroxide pellets' ;* and *'phosphorous pentoxide'* ?

4.8.26 Mazindol

4.8.26.1 Chemical Structure

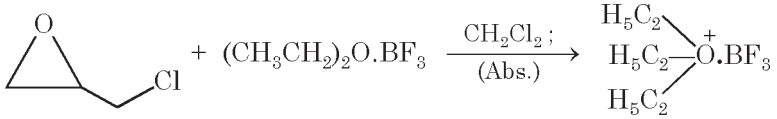


Mazindol

4.8.26.2 Synonyms. 5-(4-Chlorophenyl)-2, 5-dihydro-3H-imidazol [2, 1-a] isoindol-5-ol ; 5-(4-Chlorophenyl)-2, 3-dihydro-3-hydroxy-5H-imidazo [2, 1-*a*] isoindole ;

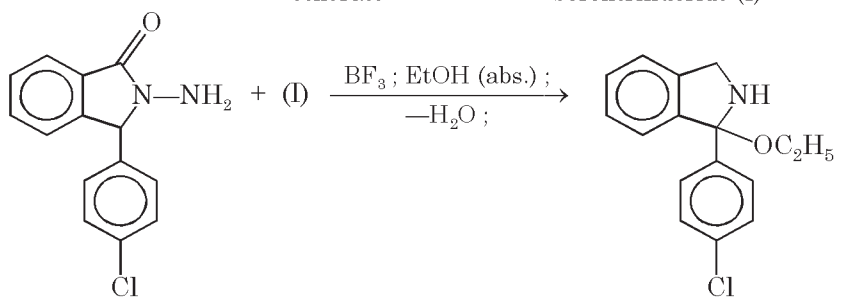
4.8.26.3 Theory

(*a*)



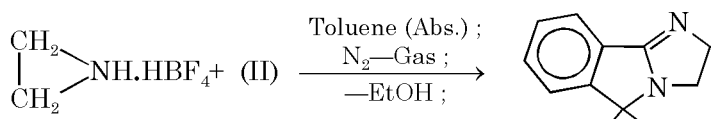
Epichlorohydrin — Boron trifloride etherate — Triethyl oxonium borontrifluoride (I)

(*b*)



3-(*p*-Chlorophenyl)phthalmidine (258.5) — 1-(*p*-Chlorophenyl)-3-ethoxy-1H-isoindole (II)

(*c*)



Ethyleneimine hydrotetrafluoroborate — Mazindol

Eqn. (*a*) shows the interaction of epichlorohydrin with boron trifluoride etherate in the presence of absolute methylene-chloride (CH_2Cl_2) to yield *triethyl oxonium borontrifluoride (I)*.

Eqn. (*b*) depicts the reaction between (I) and 3-(*p*-chlorophenyl) phthalimidine in the presence of borontrifluoride (BF_3) and absolute ethanol to give rise to the formation of 1-(*p*-chlorophenyl)-3-ethoxy-1H-isoindole (II) with the elimination of one mole of water.

Eqn. (*c*) illustrates the ring formation by the interaction of (II) with ethyleneimine hydro-tetrafluoroborate in the presence of absolute toluene, in an inert atmosphere of N_2–gas to yield mazindol with the elimination of one mole of ethanol.

4.8.26.4 Chemicals Required. Triethyloxonium borontetrafluoride : 21 g ; Borontrifluoride etherate : 23 g ; Epichlorohydrin : 11 g ; Methylene chloride (absolute) : 100 ml ; 3-(*p*-Chlorophenyl)-phthalimidine : 21 g ; Saturated soln. of Sodium Carbonate : 50 ml ; Ether : 1L ; Methylene Chloride and Hexane (1 : 1) : q.s. ; 1-(*p*-Chlorophenyl)-3-ethoxy-1H-isoindole : 1 g ; Ethylene-imine hydrotetrafluoroborate : 2 g ; Toluene Absolute : 25 ml ; Sodium carbonate solution (2 N) : 25 ml ; Acetone and Hexane (1 : 1) : q.s.

4.8.26.5 Procedure. The synthesis of mazindol may be accomplished in *two* steps, namely :

Step-I. Preparation of 1-(*p*-Chlorophenyl)-3-ethoxy-1H-isoindole :

(1) Crystalline triethyloxonium borontetrafluoride [21 g ; 0.123 mol] (prepared from 23 g borontrifluoride etherate and 11 g epichlorohydrin) is dissolved in 100 ml absolute methylene chloride. Now, 21 *g* (0.081 mol) 3-(*p*-chlorophenyl) phthalimidine is added ; and the resulting reaction mixture is stirred for a duration of 14–16 hours mechanically at an ambient temperature.

(2) The stirred solution is poured onto 50 ml solution of saturated sodium carbonate ; extracted subsequently with 500 ml ether and dried. Evaporation of solvent ether gives rise to a crude product which is recrystallized from a mixture of methylene chloride and hexane (1 : 1) to yield pure 1-(*p*-chlorophenyl)-3-ethoxy-1H-isoindole (II), 15.5 g having mp 102–103°C.

Step-II. Preparation of 5-(*p*-Chlorophenyl)-5-hydroxy-2, 3-dihydro-5H-imidazole [2, 1-a] isoindole *i.e.*, *Mazindol.*

(1) 1 g Product (II), obtained from Step-I, is mixed with 2 g ethyleneimine hydrotetrafluoroborate moistened with methylene chloride (containing approximately 0.66 g dry salt) is refluxed in 25 ml absolute toluene for 2 hours in an inert atmosphere of N_2-gas passing through the reaction mixture in a thin stream.

(2) The resulting mixture is carefully poured into a solution of sodium carbonate (2 N) 25 ml ; and extracted successively with ether. The combined ethereal solution is contacted with air for 6 days at a stretch at an ambient temperature to obtain the desired product, *mazindol.*

The crude product thus obtained is recrystallized from a mixture of acetone and hexane (1 : 1) to obtain the pure product, mp 198–199°C.

4.8.26.6 Precautions

(1) The reaction between 3-(*p*-Chlorophenyl) phthalimidine and triethyl oxonium borontrifluoride (I) is to be performed under absolute anhydrous condition with BF_3 to yield (II) by an abstraction of a mole of water. The product (II) being basic in character gets knocked out in an alkaline medium (Na_2CO_3–sat. soln.) and extracted successively with ether.

(2) The reaction between product (II) from Step-I with ethyleneimine hydrotetrafluoroborate must be carried in absolute toluene in N_2–gas for 2 hours at a stretch, made alkaline, extracted with ether successively ; and finally air must be bubbled through the ethereal layer for 6 days to yield mazindol and eliminate a mole of ethanol.

4.8.26.7 Physical Parameters. Mazindol is obtained as white crystalline solid from ethanol, mp 215–217°C. It shows uv_{max} (95% ethanol) : 223, 268.5, 272 nm ($\in$ 19000, 4400, 4400). It is found to be soluble in ethanol and insoluble in water.

4.8.26.8 Uses

(1) It is used as an anorectic, and is given orally as an adjunct to dietary measures invariably in the short-term treatment of moderate to severe obesity.

(2) It is also being investigated in the treatment of *Duchenne's muscular dystrophy**.

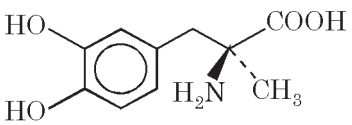
4.8.26.9 Questions for *Viva-Voce*

(1) How would you accomplish the synthesis of **'mazindol'** starting from triethyl oxonium borontrifluoride and 3-(*p*-chlorophenyl) phthalimidine ? Explain.

(2) Why is it necessary to use absolute toluene and inert N_2-gas for the formation of *'imidazol ring'* in the last step of the synthesis of mazindol ?

4.8.27 Methyldopa

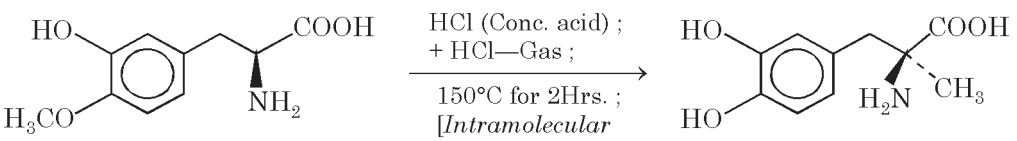
4.8.27.1 Chemical Structure



Methyldopa

4.8.27.2 Synonyms. 3-Hydroxy-α-methyl-L-tyrosine ; L-3-(3, 4-dihydroxyphenyl)-2-methylalanine ; α-Methyldopa ; L-2-amino-2-methyl-3-(3, 4-dihydroxyphenyl) propionic acid ;

4.8.27.3 Theory



3-Hydroxy-4-methoxy-phenylalanine (211.22)

(±)-Methyldopa (211.22)

The interaction of 3-hydroxy-4-methoxy phenylanine with concentrated hydrochloric acid in the presence of HCl-gas and subsequent heating at 150°C for a period of 2 hours results into an *intramolecular rearrangement* yielding a racemic mixture of **methyldopa.**

4.8.27.4 Chemicals Required. 3-Hydroxy-4-methoxyphenyl alanine : 2.5 g ; Concentrated Hydrchloric Acid (12 M) : 100 ml ; Ethanol [95% *v*/*v*] : q.s. ; Ammonium Hydroxide : q.s. ; Ether : q.s.

4.8.27.5 Procedure. The procedural details consist of **two** parts :

(*a*) Preparation of *dl*-α-methyl-3, 4-dihydroxyphenylalanine.

(*b*) Separation of L-α-methyl-3, 4-dihydroxyphenylalamine from the 'racemate'.

Part A. Preparation of *dl*-α-Methyl-3, 4-dihydroxyphenylalanine :**

(1) 2.5 g 3-Hydroxy-4-methoxyphenyl alanine was dissolved in 100 ml conc. hydrochloric acid. The resulting solution was duly saturated with hydrogen chloride (gas), and heated subsequently in a sealed tube at 150°C for a duration of 2 hours at a stretch.

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* Pseudohypertrophic muscular dystrophy marked by weakness and pseudohypertrophy of the affected musles.

** As per **Us Patent** 2, 868, 818.

(2) The resulting *'dark'* reaction mixture was concentrated to dryness under reduced pressure ; and the excess of mineral acid removed by flushing several times with ethanol.

(3) The dark residue, thus obtained, was dissolved in a minimum quantity of water. The pH of the clarified solution was adjusted to pH 6.5 with ammonium hydroxide carefully when fine crystals separated out which was filtered in a Büchner funnel under suction, washed with ethanol followed by solvent ether. The crystalline product which is a racemic mixture of methyl dopa weighed 2.24 g haivng mp ranging between 299.5–300°C with decomposition.

Part B. Separation of *dl*-α-Methyl-3, 4-dihydroxyphenyl-alanine* :

(1) 3.7 g Racemic α-methyl-3, 4-dihydroxyphenylalanine are slurried at 35°C in 10 ml of 1 N hydrochloric acid. The excess solids are filtered leaving a saturated solution containing 3.46 g racemic amino acid of which approximately 61% is present as the hydrochloride.

(2) The resulting solution is subsequently *'seeded'* at 35°C with 0.7 g hydrated L-α-methyl-3, 4-dihydroxyphenylalanine (≡ 0.62 g anhydrous material). The mixture is then cooled to 20°C in 30 minutes and aged at 20°C for 60 minutes.

(3) The separated material is isolated by filtration, washed twice with 10 ml of cold water and subsequently dried under vacuo.

The yield of the product is 1.41 g L-α-methyl-3, 4-dihydroxyphenylalanine in the form of a sequihydrate of 100% purity**.

4.8.27.6 Physical Parameters. It is obtained as L-form sesquihydrate, crystals from water. It may also be obtained as minute anhydrous crystals from methanol. It is found to be considerably hygroscopic in nature ; and gets decomposed at ~ 300°C. It exhibits specific optical rotation $[\alpha]_D^{23} - 4.0° \pm 0.5°$ (c = 1 in 0.1 M HCl). It shows uv_{max} 281 nm ($\in$ 2780). It is found to be soluble in water at 25°C : ~ 10 mg . ml^{-1}. The pH of a saturated solution (aqueous) is about 5.0. It is almost insoluble in the common organic solvents, but soluble in diluted mineral acids.

4.8.27.7 Uses

(1) It is used in the management and control of hypertension (*e.g.,* essential hypertension).

(2) Its metabolite α-methylnorepinephrine shows potent α_2–agonist activity.

4.8.27.8 Questions for *Viva-Voce*

(1) Why is it absolutely necessary to isolate the L-α-Methyl-dopa from the racemate ? Explain.

(2) What are the various latest analytical methods invariably employed for the enantiomeric separation of racemates ?

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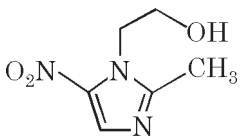
* As per US Patent 3, 158, 648.

** As determined by the rotation of the copper complex.

4.8.28 Metronidazole

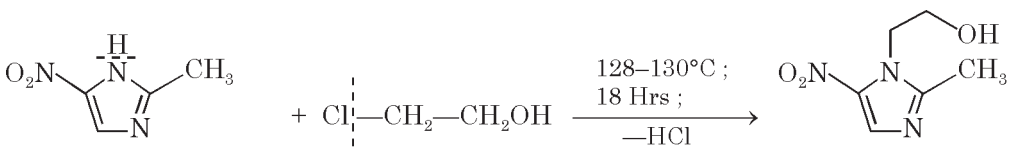
4.8.28.1 Chemical Structure



Metronidazole

4.8.28.2 Synonyms. 2-Methyl-5-nitroimidazole-1-ethanol ; 1-(2-Hydroxyethyl)-2-methyl-5-nitroimidazole ; 1-(β-Ethylol)-2-methyl-5-nitro-3-azapyrrole.

4.8.28.3 Theory



2-Methyl-5-nitro-imidazole (99) | Ethylene chlorohydrin (80.51) | Metronidazole (171.16)

The reaction between 2-methyl-5-nitroimidazole and ethylene chlorohydrin at an elevated temperatures ranging from 128° to 130°C for a period of 18 hours results into the formation of *metronidazole* with the elimination of one mole of HCl.

4.8.28.4 Chemicals Required. 2-Methyl-5-nitroimidazole : 25.4 g ; Ethylene chlorohydrin : 160 g ; Sodium Hydroxide : 20 ml ; Chloroform : 200 ml ; Ethyl acetate : 90 ml.

4.8.28.5 Procedure. The various steps involved in the synthesis are as follows :

(1) 25.4 g (0.256 mol) 2-Methyl-5-nitroimidazole is heated with ethylene chlorohydrin (160 g ; 2 mol) for a period of 18 hours at 128°–130°C.

(2) The unreacted and excess of chlorohydrin (~ 133 g) is now distilled under reduced pressure (30 mmHg).

(3) The resulting product (residue) is subsequently treated with 60 ml water (DW) and filtered. The filtrate is made alkaline by the addition of sodium hydroxide solution (d = 1.33 ; 20 ml).

(4) The alkaline solution, thus obtained, is successively extracted with chloroform (200 ml). The combined layer of chloroform is evaporated under vacuo to obtain ~ 15.5 g of a *pasty mass*.

(5) The pasty mass is recrystallized form 90 ml ethyl acetate in the presence of a small quantum of activated powdered charcoal.

The pure creamy white crystalline powder of metronidazole weighing 4.8 g, mp 158°–160°C is obtained.

4.8.28.6 Precautions

(1) In the very first step the two reactants must be heated for 18 hours at a stretch between 128°–130°C.

(2) The excess of unreacted ethylene chlorohydrin should be removed under vacuo (30 mm Hg) so that the decomposition of the final product is avoided to the maximum extent.

(3) The residue is taken up in water and made alkaline with a calculated amount of NaOH solution carefully.

4.8.28.7 Theoretical Yield/Practical Yield. The theoretical yield is calculated from the equation under theory (section 4.8.28.3) as given below :

99 g 2-Methyl-5-nitroimidazole on being reacted with 80.51 g

ethylene chlorohydrin yields Metronidazole = 171.16 g

$\therefore$ 25.4 g 2-Methyl-5-nitroimidazole shall yield Metronidazole

$$= \frac{171.16}{99} \times 25.4 = 43.91 \text{ g}$$

Hence, Theoretical Yield of Metronidazole = **43.91 g**

Reported Practical Yield = 4.8 g

Therefore, Percentage Practical Yield

$$= \frac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100$$

$$= \frac{4.8}{43.91} \times 100 = \mathbf{10.93}$$

4.8.28.8 Physical Parameters. Metronidazole is obtained as cream-coloured crystals having mp 158–160°C. Its solubility at 20°C (g/100 ml) : water 1.0 ; ethanol 0.5 ; ether < 0.05 ; and chloroform < 0.05. It is found to be sparingly soluble in dimethyl formamide (DMF) and soluble in diluted acids. The pH of a saturated aqueous solution stands at 5.8.

4.8.28.9 Uses

(1) Metronidazole long has been the drug of choice for the treatment of *trichomoniasis* and more recently in combination with idoquinol for the treatment of symptomatic *amebiasis.*

(2) It is also the drug of choice for the treatment of *Dracunculus* (guinea worm).

(3) It is the alternative drug to treat *giardiasis, balantidiasis, blastocystitis,* and infections by *Entameba polecki.*

(4) It is used widely for the treatment and prophylaxis of infections caused by anaerobic bacteria.

(5) It is a drug of choice against GI strains of *Bacteroides fragilis* ; and vaginal infections caused by *Gardnerella vaginalis.*

(6) It has been used successfully in the treatment of antibiotic-associated *psedomembranous colitis.*

(7) It is also useful in **Crohn's disease*.**

4.8.28.10 Questions for *Viva-Voce*

(1) Why is the reaction mixture made alkaline after the removal of unreacted ethylene chlorohydrin ? Explain.

(2) How would you account for the **'metronidazole'** as one of the most potent *anti-protozoal agents ?*

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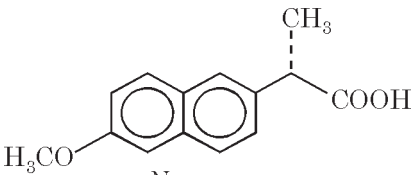
* **Crohn's Disease.** The term commonly used for a number of chronic inflammatory diseases of the gastrointestinal tract (GIT).

4.8.29 Naproxen

4.8.29.1 Chemical Structure

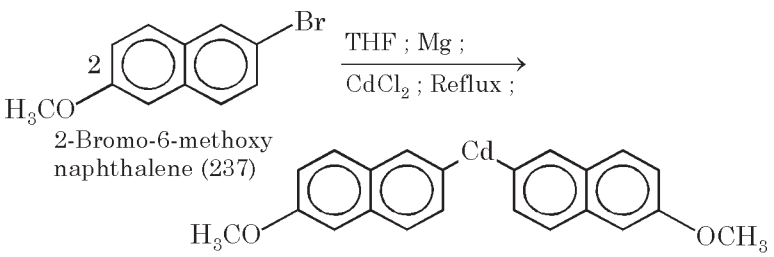


Naproxen

4.8.29.2 Synonyms. (S)-6-Methoxy-α-methyl-2-naphthaleneacetic acid ; *d*-2-(6-Methoxy-2-naphthyl) propionic acid.

4.8.29.3 Theory

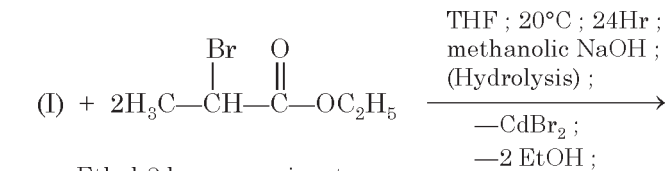
(*a*)



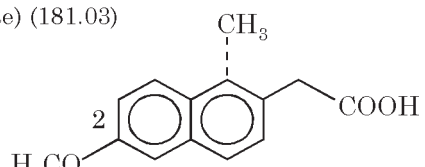
2-Bromo-6-methoxy naphthalene (237)

Di-(6-methoxy-2-naphthyl) cadmium (I)

(*b*)



Ethyl-2-bromopropionate (*or*-Ethyl-α-bromopropionate) (181.03)



Naproxen (230.26)

Eqn. (*a*) represents the interaction between 2-bromo-6-methoxy naphthalene and cadmium chloride in the presence of fresh magnesium turnings and tetrahydrofuran (THF) followed by reflux to give rise to the formation of one mole of di-(6-methoxy-2-naphthyl) cadmium (I).

Eqn. (*b*) shows the interaction between (I) and two moles of ethyl-2-bromopropionate in the presence of THF, at 20°C for 24 hours followed by hydrolysis in the presence of methanolic NaOH to yield the desired product *naproxen* with the elimination of one mole of $CdBr_2$ and two moles of ethanol.

4.8.29.4 Chemicals Required. 2-Bromo-6-methoxynaphthalene : 24 g ; Tetrahydrofuran (THF) : 450 ml ; Magnesium turnings (Fresh) : 2.5 g ; Cadmium chloride : 20 g ; Ethyl-2-bromopropionate : 18 g ; Methanolic NaOH solution [5% (w/v)] : 200 ml ; Ether : q.s. ; Acetone : Hexane (1 : 1) : q.s.

4.8.29.5 Procedure. The different steps followed sequentially are as stated below* :

(1) A solution of 24 g 2-bromo-6-methoxynaphthalene in 300 ml THF is poured gradually to 2.5 g fresh magnesium turnings and 100 ml THF at reflux temperature (~ 66°C).

(2) Once the addition is complete, 20 g cadmium chloride is added ; and the resultant mixture is refluxed for 10 minutes to yield a solution of di-(6-methoxy-2-naphthyl) cadmium (I).**

(3) A solution of 18 g ethyl-2-bromopropionate in 20 ml THF is now added to the previously cooled reaction mixture obtained in step (2). After allowing to keep the resulting mixture at 20°C for a duration of 24 hours, the product is subjected to hydrolysis by adding carefully 200 ml of methanolic NaOH solution, followed by heating to reflux for 60 minutes.

(4) The resulting mixture is then diluted with excess of sulphuric acid (1 N) to acidic condition ; and extracted with ether successively. The ethereal layer is separated, evaporated to dryness.

(5) The residue is recrystallized from a mixture of acetone and hexane (1 : 1) to give rise to the ultimate yield of the desired product, *naproxen*, to the extent of 16.66 g, mp 152–154°C.

4.8.29.6 Precautions

(1) Step (3) is very crucial in the synthesis of *'naproxen'* and each step must be followed rigidly.

(2) In step (4) the bulk of the ether from the combined ethereal extract must be removed in a thin-film rotary evaporator carefully.

4.8.29.7 Theoretical Yield/Practical Yield. The theoretical yield may be calculated from the equation under theory (section 4.8.29.3) as stated under :

237 g 2-Bromo-6-methoxy naphthalene after a sequence of reactions

yield Naproxen = 230.26 g

∴ 24 g 2-Bromo-6-methoxy naphthalene shall yield Naproxen

$$= \frac{230.26}{237} \times 24 = 23.32 \text{ g}$$

Hence, Theoretical yield of Naproxen = **23.32 g**

Reported Practical Yield = 16.66 g

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* US Patent 3,658,858.

** Compound (I) obtained in step (2) may be separated by conventional chromatography ; however, separation is otherwise quite unnecessary.

Therefore, Percentage Practical Yield $= \dfrac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100$

$= \dfrac{16.66}{23.32} \times 100 = \mathbf{71.18}$

4.8.29.8 Physical Parameters. Naproxen is obtained as bitter crystals from acetone hexane having mp 152–154°C. It has specific optical rotation $[\alpha]_D$ + 66° (in chloroform). It is found to be soluble in 25 parts ethanol (96%); 20 parts methanol ; 15 parts chloroform ; 40 parts ether ; and almost insoluble in water. It has apparent pKa 4.15.

4.8.29.9 Uses

(1) It is indicated for relief of symptoms of rheumatiod arthritis, both of acute flares and long-term management of the disease.

(2) It is used to relieve mild-to-moderate postoperative pain as well as postpartum pain, primary dysmenorrhea, orthopedic pain, headache, and visceral pain associated with cancer.

(3) Its analgesic actions are fairly comparable with those of *aspirin* or *indomethacin.*

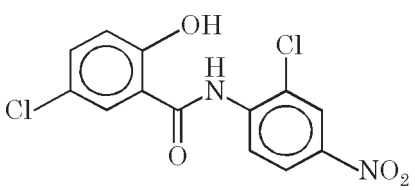
4.8.29.10 Questions for *Viva-Voce*

(1) How would you synthesize *'naproxen'* starting form 2-bromo-6-methoxy naphthalene ?

(2) What are the specific therapeutic applications of naproxen ?

4.8.30 Niclosamide

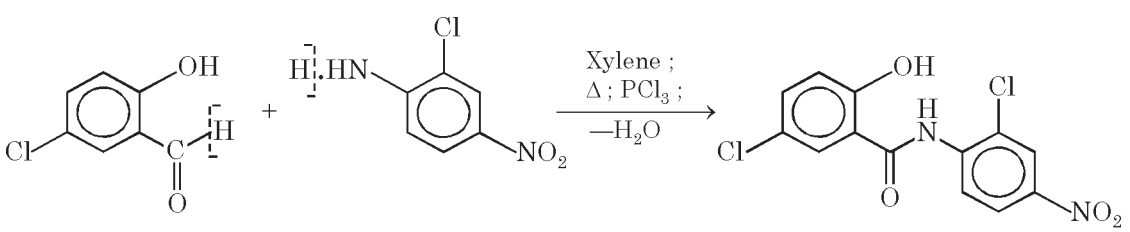
4.8.30.1 Chemical Structure



Niclosamide

4.8.30.2 Synonyms. 5-Chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxy-benzamide ; 5-Chloro-salicyloyl-(*o*-chloro-*p*-nitranilide) ; N-(2′-Chloro-4′-nitrophenyl)-5-chlorosalicylamide.

4.8.30.3 Theory



5-Chloro-salicylic acid (172.5) | 2-Chloro-4-nitro aniline (172.5) | Niclosamide (327.12)

The interaction between 5-chlorosalicylic acid and 2-chloro-4-nitro aniline in the presence of xylene, phosphorous tri-chloride and heating results into the formation of niclosamide with the elimination of one mole of water.

4.8.30.4 Chemicals Required. 5-Chlorosalicylic acid : 17.25 g ; 2-Chloro-4-nitroaniline : 20.9 g ; Xylene : 250 ml ; Phosphorous trichloride (PCl_3) : 5 g ; Ethanol : q.s.

4.8.30.5 Procedure. The various steps involved in the synthesis of niclosamide are as stated below :

(1) 17.25 g (0.1 mol) 5-Chlorosalicylic acid and 20.9 g (0.12 mol) 2-chloro-4-nitroaniline are dissolved carefully in 250 ml pure xylene in a 500 ml round bottom flask fitted with a double surface condenser.

(2) The reaction mixture is boiled on a heating mantle and are introduced in small lots at intervals 5 g pure PCl_3 from the top end of the condenser. Heating is continued for two further hours.

(3) The reaction mixture is allowed to cool down when the crude crystals of niclosamide start separating out. Filter the crude product in a Büchner funnel under suction.

The crude product is recrystallized from ethanol to yield 26.5 g having mp 233°C.

4.8.30.6 Precautions

(1) Both *xylene* and *phosphorous trichloride* should be freshly distilled and under perfectly anhydrous conditions to yield better product and maximum yield.

(2) The crude product may be recrystallized from a minimum quantity of ethanol.

4.8.30.7 Theoretical Yield/Practical Yield. The theoretical yield is usually calculated from the equation given under theory (section 4.8.30.3) as stated below :

172.5 g 5-Chloro-salicylic acid on being treated with 2-chloro-

4-nitroaniline yields Niclosamide = 327.12 g

$\therefore$ 17.25 g 5-Chloro-salicylic acid shall yield Niclosamide $= \frac{327.12}{172.5} \times 17.25 = 32.71$ g

Hence, Theoretical Yield of Niclosamide = **32.71 g**

Reported Practical Yield = 26.50 g

Therefore, Percentage Practical Yield $= \frac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100$

$= \frac{26.5}{32.71} \times 100 =$ **81.01**

4.8.30.8 Physical Parameters. Niclosamide is obtained as pale yellow crystals having mp 225–230°C. It is found to be practically insoluble in water ; and sparingly soluble in ethanol, ether and chloroform.

4.8.30.9 Uses. It is a potent *anthelminthic* especially effective against the *cestodes** that infect humans.

4.8.30.10 Questions for *Viva-Voce*

(1) What is the significance of PCl_3 in the synthesis of *niclosamide ?*

(2) What are the functional moieties present in the molecule of *'miclosamide'* that exert anthelminthic activity against the cestodes in humans ?

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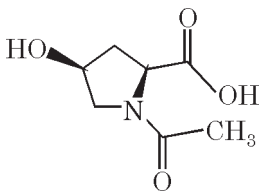
* **Cestodes.** A subclass of the class *Cestoidea,* phylum *Platyhelminthes,* which includes the **tapeworms.**

4.8.31 Oxaceprol

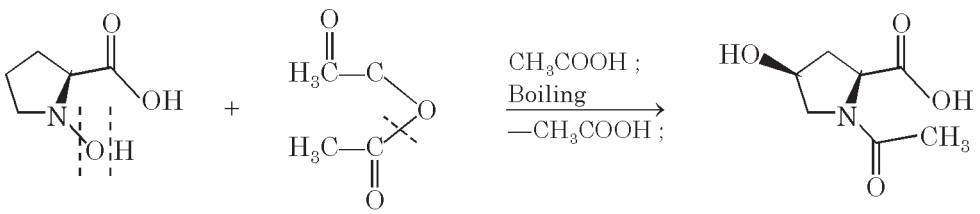
4.8.31.1 Chemical Structure



Oxaceprol

4.8.31.2 Synonyms. *trans*-1-Acetyl-4-hydroxy-L-proline ; 4-Hydroxy-N-acetylproline ; 1-Acetyl-4-hydroxy-2-pyrrolidine carboxylic acid.

4.8.31.3 Theory



1-Hydroxy-proline (131.13) | Acetic anhydride (102.09) | Oxaceprol (173.7)

The reaction between 1-hydroxy proline and acetic anhydride in a medium of glacial acetic acid upon boiling yields a mole of oxaceprol with the elimination of one mole of acetic acid. The hydroxy moiety gets hooked onto the C-4 atom ; and the arrangement of the *acetyl function* at N-1 and *carboxylic function* at C-2 are *trans*-to one another **spatially** (*i.e., existing in space*).

4.8.31.4 Chemicals Required. 1-Hydroxy proline : 16.7 g ; Glacial acetic acid : 650 ml ; Double-distilled/Rectified Acetic anhydride : 13.7 mol ; Anhydrous Toluene : 40 ml ; Anhydrous Acetone : 300 ml.

4.8.31.5 Procedure. The various steps adopted in the synthesis are described below in a sequential manner :

(1) 16.7 g (0.127 mol) 1-Hydroxyproline are dissolved in 400 ml of pure boiling glacial acetic acid in a 1L dry round bottom flask fitted with an air condenser and an efficient mechanical stirrer.

(2) While the vigorous agitation and boiling is in progress, a mixture of 13.7 ml (0.134 mol) acetic anhydride and 250 ml pure glacial acetic acid is added slowly over a duration of 25–30 minutes.

(3) Now, allowing the stirring to continue vigorously as earlier, the contents of the flask are cooled by simply circulating fresh air externally around the flask unless and until the temperature of the reaction mixture is brought down to approximately 34 ± 2°C.

(4) The large excess of glacial acetic acid is removed by using a *thin-film rotary evaporator,* without exceeding the temperature to go beyond 35°C in any case, by subjecting the evaporation under a vacuum of nearly 15 mm Hg.

(5) After a period of 60 minutes 20 ml of anhydrous toluene followed by 10 ml of anhydrous acetone are introduced into the resulting residue obtained from step (4). The resulting mixture is homogenized and concentrated again as stated above during 30 minutes.

(6) Again the process is repeated once more by adding 25 ml acetone followed by 20 ml toluene, concentrating the product to such an extent as to obtain an *amber-coloured crystallized paste.*

(7) Finally, 30 ml anhydrous acetone is added to the residue, and stirring is carried out until the oily fraction encirculing the crystals is dissolved more or less completely. The emerging solid product is cooled in a freezer overnight, centrifuged, washed twice with anhydrous acetone, and eventually dried under vacuum.

The crude product is recrystallized from dry acetone to obtain 16.31 g of pure oxaceprol having mp 133–134°C.

4.8.31.6 Precautions

(1) The reaction must be carried out in absolute dry conditions.

(2) All solvents used in the synthesis must be ensured to be from even traces of moisture.

(3) The procedural steps (4) through (7) are very critical and, therefore, must be performed with utmost care.

4.8.31.7 Theoretical Yield/Practical Yield. The theoretical yield of oxaceprol may be calculated from the equation under theory (section 4.8.31.3) as given under :

131.13 g 1-Hydroxyproline on reacting with acetic anhydride yields Oxaceprol = 173.17 g

$\therefore$ 16.7 g 1 Hydroxyproline shall yield Oxaceprol $= \frac{173.17}{131.13} \times 16.7 = 22.05$ g

Hence, Theoretical Yield of Oxaceprol = **22.05 g**

Reported Practical Yield = 16.31 g

Therefore, Percentage Practical Yield $= \frac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100$

$= \frac{16.31}{22.05} \times 100 =$ **73.97**

4.8.31.8 Physical Parameters. Oxaceprol is usually obtained as crystals from acetone having mp 133–134°C. It shows specific optical rotation $[\alpha]_D^{20} - 116.5°$ ($c = 3.2$) and $[\alpha]_D^{18} - 119.5°$ ($c = 3.75$). It is found to be very soluble in ethanol ; soluble in water and methanol ; and insoluble in ether and chloroform.

4.8.31.9 Uses

(1) It is used as an anti-inflammatory drug.

(2) It also finds its application as vulnerary (*i.e.,* an agent used to promote wound healing process).

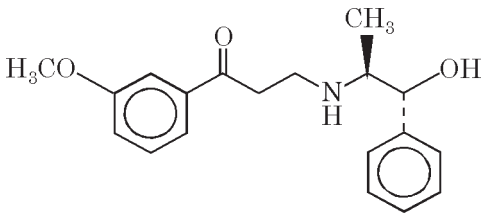
4.8.31.10 Questions for *Viva-Voce*

(1) How would you explain the *'mechanism'* for the synthesis of oxaceprol ?

(2) The *trans*-**isomer** is active therapeutically and not the *cis*-**isomer.** How do you explain the spatial arrangement *vis-a-vis* the therapeutic response of oxaceprol ?

4.8.32 Oxyfedrine

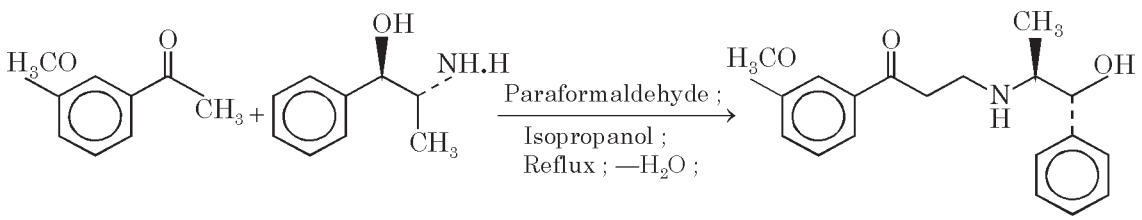
4.8.32.1 Chemical Structure



Oxyfedrine

4.8.32.2 Synonyms. [R-(R*, S*)]-3-[(2-Hydroxy-1-methyl-2-phenylethyl) amino]-1-(3-methoxyphenyl)-1-propanone ; L-(1-Hydroxy-1-phenyl-2-propylamino)-1-(*m*-methoxyphenyl)-1-propanone ; Oxyphedrine.

4.8.32.3 Theory



m-Methoxy acetophenone (150) | L-Norephedrine (151.21) | Oxyfedrine (313.40)

The synthesis of *Oxyfedrine* is based on the *Mannich Reaction* (see under *'Organic Name Reactions'* part 'J') wherein one mole each of a *'ketone' i.e., m*-methoxy acetophenone reacts with a *'primary amine' i.e.,* L-norephedrine in the presence of paraformaldehyde to give rise to a product with an additional —CH_2— moiety derived from formaldehyde (or paraformaldehyde) *i.e.,* oxyfedrine with the elimination of a mole of water.

4.8.32.4 Chemicals Required. *meta*-Methoxy acetophenone : 45 g ; Paraformaldehyde : 8 g ; L-Norephedrine : 30.25 g ; Isopropanol HCl solution (pH 4.0) : 135 ml ; Methanol : q.s.

4.8.32.5 Procedure. The various steps followed in the synthesis of *oxyphedrine* are as given below :

(1) 45 g (0.3 mol) *meta*-Methoxy acetophenone, 8 g paraformaldehyde and 30.25 g L-norephedrine were mixed thoroughly with isopropanol HCl solution (pH 4.0) in a 500 ml round bottom flask ; and the reaction mixture refluxed for 4 hours at a stretch.

(2) The resulting reaction mixture was cooled in a refrigerator to obtain crystals that was filtered subsequently in a Büchner funnel under suction.

The crude oxyfedrine hydrochloride (*i.e.,* L-Form HCl was duly recrystallized from methanol to obtain 64.5 g of pure product having mp 192–194°C.

4.8.32.6 Precautions

(1) All reagents and paraformaldehyde should be in perfect *'anhydrous conditions'* to afford an effective *'Mannich Reaction'* with an abstraction of a mole of water.

(2) Acidified isopropanol at pH 4.0 must be used as a medium for the reflux of reaction mixture for 4 hours.

4.8.32.7 Theoretical Yield/Practical Yield. The theoretical yield is usually calculated from the equation under theory (section 4.8.32.3) as stated under :

150 g *m*-Methoxy acetophenone on treatment with L-norephedrine and paraformaldehyde yields Oxyfedrine = 313.40 g

$\therefore$ 45 g *m*-Methoxy acetophenone shall yield Oxyfedrine $= \frac{313.40}{150} \times 45 = 94.02$ g

Hence, Theoretical yield of Oxyfedrine = **94.02 g**

Reported Practical Yield = 64.5 g

Therefore, Percentage Practical Yield $= \frac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100$

$= \frac{64.5}{94.02} \times 100 =$ **68.60**

4.8.32.8 Physical Parameters. The crystals of L-form Oxyfedrine Hydrochloride from methanol has mp ranging between 192-194°C.

4.8.32.9 Uses

(1) It exerts vasodilator properties and is used in angina pectoris, heart failure and myocardial infarction.

(2) It is also used in the management and treatment of coronary insufficiency.

4.8.32.10 Questions for *Viva-Voce*

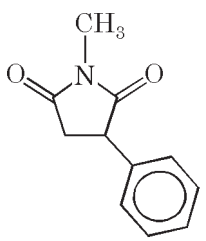
(1) What is Mannich Reaction ? Explain.

(2) How do we get an additional —CH_2-— moiety in the side chain in all Mannich reactions ?

(3) What is 'paraformaldehyde' ? Why do we prefer to use paraformaldehyde than formalin (HCHO) in a Mannich Reaction ?

4.8.33 Phensuximide

4.8.33.1 Chemical Structure

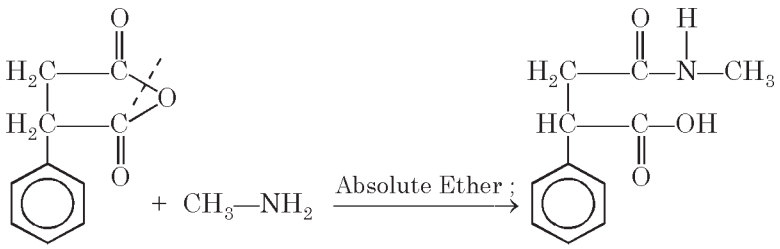


Phensuximide

4.8.33.2 Synonyms. 1-Methyl-3-phenyl-2, 5-pyrrolidinedione ; N-Methyl-2-phenyl-succinimide ; N-Methyl-α-phenyl-succinimide.

4.8.33.3 Theory

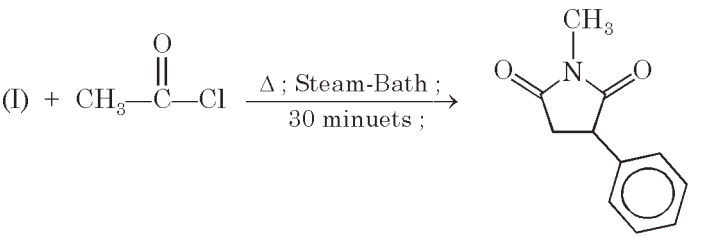
(*a*)



Phenyl succinic anhydride methyl amine (164)

β-N-Methylphenyl-succinamic acid (I)

(*b*)



Acetyl chloride

Phensuximide (189.21)

The synthesis of *Phensuximide* proceeds usually in *two* steps, namely :

(*i*) Preparation of β-N-Methylphenyl succinamic acid, and

(*ii*) Preparation of N-Methyl-α-phenyl succinimide (*i.e.,* Phenusximide).

Eqn. (a). Illustrates the reaction between phenylsuccinic anhydride and methyl amine in the presence of absolute dry ether to give rise to the formation of (3-N-methylphenyl-succinamic acid (I).

Eqn. (b). Shows the interaction of compound (I) with acetyl chloride at an elevated temperature where upon closure of ring takes place to yield phensuximide.

4.8.33.4 Chemicals Required. Phenylsuccinic anhydride : 10 g ; Absolute Ether : 350 ml ; Dry Methylamine : q.s. ; Ethanol : q.s. ; β-N-Methylphenyl succinamic acid : 9 g ; Acetyl chloride : 200 ml ; Anhydrous $MgSO_4$: q.s.

4.8.33.5 Procedure. The synthesis of *'phensuximide'* is carried out in *two* steps, namely :

Step-I. Preparation of (β-N-Methylphenyl succinamic Acid) :

(1) 10 g (0.164 mol) Phenylsuccinic anhydride is dissolved in 250 ml absolute (dry) ether and the solution is treated with dry methyl amine *until a precipitate ceases to form.* After allowing it to stand for a duration of 30 minutes, the ether is decanted off carefully ; and the residue is washed with 40 ml of distilled water by decantation.

(2) The resulting mixture is filtered and the precipitate washed with 10 ml of water (Crop-1). The filtrate is acidified with dilute HCl carefully to obtain a white precipitate (Crop-2). After drying it weighs approximately 8 g (mp 136°–140°C). The two precipitates are combined and recrystallized from aqueous ethanol to yield β-N-methylphenyl succinamic acid (I) that melts at 158°–160°C.

Setp II. Preparation of N-Methyl-α-phenylsuccinimide (i.e., Phensuximide) :

(1) 9 g Compound (I), obtained from Step I, and 200 ml redistilled acetyl chloride are heated together on a steam-bath for 30 minutes with frequent swirling of the contents.

(2) The excess of acetyl chloride is duly removed by distillation under vacuo ; and 50 ml of distilled water is added to the rather thick-residue.

(3) After allowing the hydrolysis of the excess acetyl chloride the water is decanted off carefully ; and the yellow residue is dissolved in 75 ml of dry ether.

(4) The resulting yellow-coloured solution is treated with charcoal (activated) twice ; and subsequently dried over anhydrous magnesium sulphate.

(5) When partial evaporation of ether is affected, a white solid precipitates out, which is nothing but *phensuximide* weighing 4.2 g having mp 71°–73°C.

4.8.33.6 Precautions

(1) In Step I, dry methyl amine gas is required to be passed through the reaction mixture slowily till the formation of further precipitates ceases completely. This step should preferably be carried out in an efficient fuming cupboard.

(2) In Step II, the excess of acetyl chloride need to be removed by distillation, while the residual acetyl chloride must be hydrolyzed with water and decanted of before proceeding ahead for the recovery of phensuximide.

4.8.33.7 Physical Parameters. Phensuximide may be obtained as fine crystals from hot 95% ethanol having mp ranging between 71°-73°C. It is found to be slightly soluble in water (about 4.2 mg mL^{-1} at 25°C) ; readily soluble in ethanol and methanol. The aqueous solutions are observed to be fairly stable at pH 2.8 ; however, hydrolysis invariably sets in under more alkaline conditions.

4.8.33.8 Uses

(1) It is mostly used as an antiepileptic agent.

(2) It may also be used for myoclonic seizures.

(3) It is also employed in the treatment of absence (petitmal) seizures.

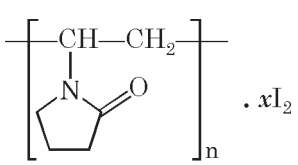
4.8.33.9 Questions for *Viva-Voce*

(1) How would you accomplish the synthesis of '**phensuximide**' starting from phenyl succinic anhydride ? Explain.

(2) What measures would you take to get rid of '*acetyl chloride*' completely from the reaction mixture before proceeding to the isolation of phensuximide ? Explain.

4.8.34 Povidone-Iodine

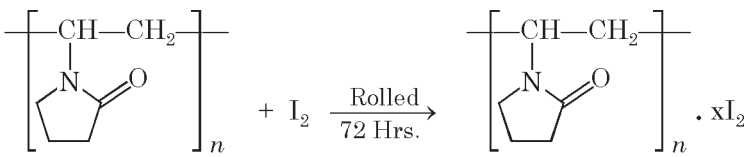
4.8.34.1 Chemical Structure



Povidone-iodine

4.8.34.2 Synonyms. 1-Ethenyl-2-pyrrolidinone homopolymer compound with iodine ; 1-Vinyl-2-pyrrolidinone polymers, iodine complex ; Iodine-polyvinylpyrrolidone complex ; Polyvinylpyrrolidone-iodine complex ; PVP-I ; Betadine.

4.8.34.3 Theory



Polyvinylpyrrolidone Iodine Povidone-iodine

Povidone-iodine may be prepared by the physical contact of polyvinylpyrrolidone having a K value of 90 and water content between 2-3%, with finely pulverized iodine crystals over a span of three days.

4.8.34.4 Chemicals Required. Polyvinyl pyrrolidone [K value = 90] : 12 g ; Water content : 2-3%] : 12 g ; Iodine crystals : 6 g.

4.8.34.5 Procedure. The steps adopted for the preparation of povidone-iodine are as follows :

(1) 12 g Polyvinylpyrrolidone is added to 6 g finely pulverized iodine crystals in a perfectly dry glass bottle previously containing a few pebbles and glass beads.

(2) The glass bottle was made to roll for three full days on a '*Roller Mill*', with intermittent manual stirring the reactants in order to loosen the substance that might have formed as a cake along the inner sides of the glass bottle. An analysis carried out must show that the resulting product thus obtained usually contained *35.4% total iodine* and *31.9% available iodine*.

(3) The resulting material was subjected to heating at 95°C for 64 hours exactly, in a closed glass bottle with occasional stirring. After due completion of this treatment, the subsequent analysis showed that the material contained **35.3% total iodine** and **25.7% available iodine***.

4.8.34.6 Precautions

(1) Intermittent manual stirring to loosen the formation of caked materials in step (2) is very essential and important.

(2) Heating at 95°C for 64 hours is equally important in Step (3) to obtain a consistent and stable product.

4.8.34.7 Physical Parameters. Povidone-iodine is obtained as yellowish-brown, amorphous powder with slight typical characteristic odour. The aqueous solutions have a pH ~ 2 ; it may be made **more neutral (but less stable)** by the addition of sodium bicarbonate. It is found to be soluble in ethanol and water ; almost insoluble in chloroform, carbon tetrachloride, solvent ether, hexane ; and acetone. Interestingly, its solutions do not respond to the familiar 'blue colour' starch-test, when prepared even freshly.

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*U.S. Patent 2,706,701.

4.8.34.8 Uses

(1) It is an '*iodophore*' which is mostly used as a disinfectant and antiseptic exclusively for the treatment of contaminated wounds.

(2) It is also employed in preoperative preparations of the skin and mucous membranes as well as for the disinfection of equipment(s).

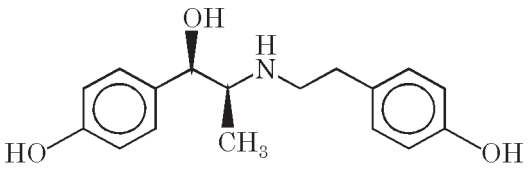
4.8.34.9 Questions for *Viva-Voce*

(1) Why is it necessary to heat the reactants to get the final product, povidone-iodine ?

(2) How would you account for the lowering of available iodine from 31.9% to 25.7% in cold and heated products ? Explain.

4.8.35 Ritodrine

4.8.35.1 Chemical Structure

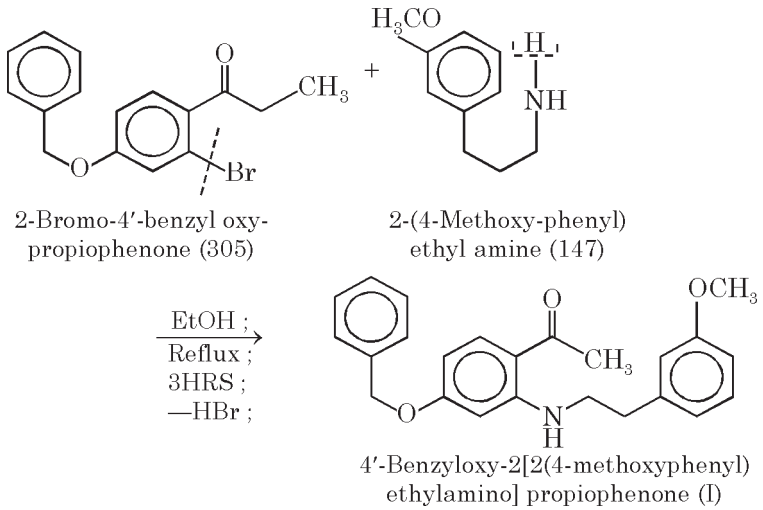


Ritodrine

4.8.35.2 Synonyms. (R*, S*)-4-Hydroxy-α-[1-[[2-(4-hydroxyphenyl) ethyl] amino]ethyl] benzenemethanol ; 1-(4-Hydroxyphenyl)-2-[2-(4-hydroxyphenyl) ethyl amino] propanol.

4.8.35.3 Theory

(*a*)

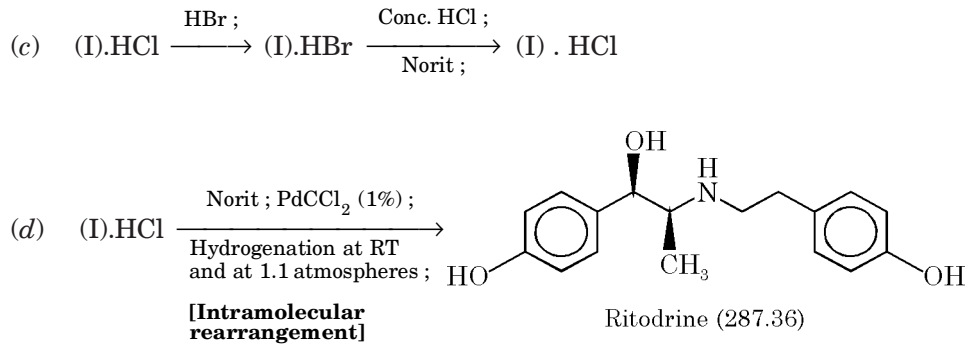


2-Bromo-4′-benzyl oxy-propiophenone (305)

2-(4-Methoxy-phenyl) ethyl amine (147)

4′-Benzyloxy-2[2(4-methoxyphenyl) ethylamino] propiophenone (I)

(*b*) (I) $\xrightarrow[\text{[NORIT : Carbon Amorphous]}\ \text{Hydrogenation at 1.1 atmospheres}]{\text{EtOH ; } PdCl_2\ (1\%)\ ;}$ (I).HCl [HCl–Salt of (I)]



The synthesis of '*ritodrine*' is accomplished in *four* steps, namely :

Eqn. (*a*) shows the reaction between 2-bromo-4′-benzyloxypropiophenone and 2-(4-methoxyphenyl)-ethylamine in the presence of ethanol to yield an intermediate 4′-benzyloxy-2[2[4-methoxy-phenyl) ethylamino] propiophenone (I).

Eqn. (*b*) depicts the conversion of compound (I) into its corresponding hydrochloride salt by treatment with palladium chloride (1%) and hydrogenation at 1.1 atmospheres, (I) HCl.

Eqn. (*c*) shows the purification mode of (I) HCl through (I) HBr to (I) HCl again.

Eqn. (*d*) illustrates the final important step whereby the purified (I) HCl salt undergoes '*intramolecular rearrangement*' in the presence of $PdCl_2$ (1%) and hydrogenation at room-temperature at 1.1 atmospheres to result into the formation of one mole of *ritodrine*.

4.8.35.4 Chemicals Required. 2-Bromo-4′-benzyloxy propiophenone : 44 g ; 2-(4-Methoxyphenyl) ethylamine : 44 g ; Ethanol : 750 ml ; Hydrochloric Acid (2 M) : q.s. ; 4′-Benzyloxy-2[2[4-methoxyphenyl) ethylamino] propiophenone (I) : 12 g ; Palladium chloride [1% (w/v)] : 50 ml ; Norit : 6 g ; Hydrobromic acid (48%) : 30 ml ; Conc. Hydrochloric Acid (12 M) : q.s. ; Potassium chloride [1% (w/v)] : 8 ml ; Dilute Ammonia solution : q.s. ; Ether : q.s.

4.8.35.5 Procedure. The various steps involved in the synthesis are enumerated below in a sequential manner :

(1) A solution of 44 g (0.144 mol) 2-bromo-4′-benzyloxy propiophenone and 44 g (0.3 mol) 2-(4-methoxyphenyl) ethylamine in 270 ml ethanol was refluxed for a duration of 3 hours on a heating mantle. The excess of ehanol was distilled off under vacuo, and the resulting concentrate was mixed with ether. The ensuing crystallizate was removed by suction in a Büchner funnel ; and the filtrate was adequately mixed with an excess of 2 M.HCl. Thus, the corresponding hydrochloride salt of (I) crystallized out slowly. The resulting crude product was recrystallized from dilute alcohol with an yield of 25.5 g and mp ranging between 217°-218°C, [(I).HCl].

(2) 12 g of (I).HCl obtained from step (1) was dissolved in a mixture of 300 ml ethanol and 90 ml water in a 2 L round bottom flask. To the resulting solution were added 42 ml 1% $PdCl_2$ solution and 3.9 g Norit (*Carbon amorphous*). The solution was duly hydrogenated at room temperature and at a pressure of 1.1 atmospheres until approximately 760 ml hydrogen had been taken up. The catalyst was removed by filtration and the solvent present in the filtered solution was evaporated entirely under reduced pressure.

(3) The resulting residue, which consisted of the hydrochloride of (I), was mixed with 30 ml of a 48% HBr solution and the mixture was boiled until no methyl bromide developed any more, which was the case after nearly 45 minutes. The reaction mixture was stored in the refrigerator (0-10°C) overnight, after which the hydrobromide of (I) crystallized out [Eqn. (*c*)]. It was subsequently sucked off and reconverted into its HCl salt by again dissolving the resulting substance in water, discolouring the solution with a little Norit, and then adding an equal volume of conc. HCl (12 M). Thus, the HCl salt of (I) got crystallized. The yield of the product was 9.6 g, mp 136°-138°C. After this product had been recrystallized once again it was reduced to the amino alcohol.

(4) For this purpose, a solution of 3.2 g of the HCl in 160 ml DW was provided with 0.5 g of Norit and 8 ml 1% $PdCl_2$; and the mixture was hydrogenated at room temperature and at a pressure of 1.1 atmospheres until no hydrogen was taken up any more. The catalyst was now removed by filtration, after which the filtrate was concentrated in vacuo. To the concentrated solution of the reduced product was then added an excess of dilute ammonia, as a result of which the base of the desired product, *ritodrine*, precipitated as a hard mass. After the mixture had been kept in the refrigerator for 6-8 hours, the product was sucked off, washed with water and dried in vacuo.

The final product of ritodrine was obtained as a resinous mass upto 2.3 g, mp 88°-90°C.

4.8.35.6 Precautions

(1) In general, most of the evaporations of solvents etc., must be carried out at reduced pressure so as to avoid any possible deterioration of the final product.

(2) Norit *i.e.,* an amorphous carbon should only be used as a decolourising agent in this synthises.

4.8.35.7 Physical Parameters. Ritodrine is a base and obtained as a resinous mass having mp ranging between 88-90°C.

4.8.35.8 Uses

(1) It is used just like salbutamol *i.e.,* as a bronchodilator.

(2) It decreases uterine contractions and is often employed to arrest premature labour *i.e.,* as a *'tocolytic'*.

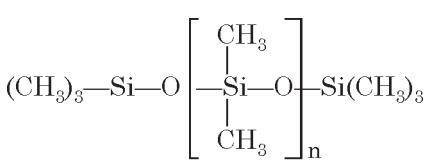
4.8.35.9 Questions for *Viva-Voce*

(1) How would you accomplish the synthesis of '*ritodrine*' from *ab initio* ? Explain.

(2) Explain the terminologies *tocolytic* and *Norit*.

4.8.36 Simethicone

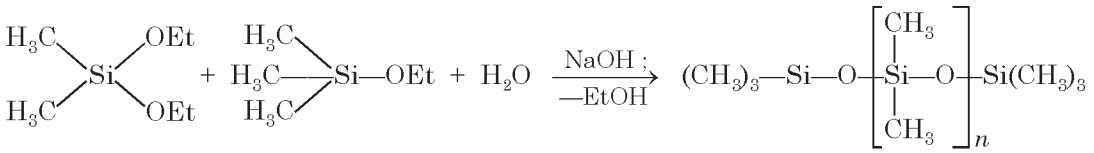
4.8.36.1 Chemical Structure



Simethicone

4.8.36.2 Synonyms. Dimethyl polysiloxane ; Dimetico ; Dimethicone ; Polydimethylsiloxane; Mixture with SiO_2—Simethicone or Activated Dimethicone ;

4.8.36.3 Theory



Dimethyldiethoxy silane (148) | Trimethylethoxy silane (118) | Water (18) | Simethicone

The interaction between dimethyldiethoxy silane and trimethylethoxy silane with water, in the presence of 1 NaOH per 100 silicon atoms, gives rise to the formation of simethicone with the elimination of a calculated amount of ethanol. *The presence of NaOH, as a catalyst, ensures the formation of only straight chain polymers*.

4.8.36.4 Chemicals Required. Dimethyl diethoxy silane : 139.3 g ; Timethyl ethoxy silane : 111 g ; Distilled water : 25.4 g ; Sodium hydroxide : 0.75 g ; Hydrochloric acid (20%) : 55.5 ml.

4.8.36.5 Procedure. The different steps followed in the synthesis of simethicone are stated below in a sequential manner :

(1) In a 1 L 3-necked round bottom flask, duly fitted with a double-surface reflux condenser, mechanical agitator and thermometer, were placed 139.3 g (0.941 mol) of freshly distilled dimethyl diethoxy silane and 111 g (0.941 mol) trimethyl ethoxy silane.

(2) To the resulting solution was added 25.4 g (1.411 mol) distilled water containing 0.75 g sodium hydroxide. The resulting mixture was first shaken thoroughly and then heated to 40°C. The temperature continued to rise for nearly 60-70 minutes. After adding 5 ml (~ 20% excess) more water, the above mixture was refluxed for a duration of 2 hours and then allowed to stand overnight at an ambient temperature.

(3) The alcohol was distilled off, until the temperature reached 100°C. Thus, about 170.66 g *distillate* was collected (theoretically equivalent to 143 g). The alcoholic content was carefully powered into 682.64 g (~ 4 times its volume) of water placed in a beaker ; when an '**isoluble oil**' got separated (45.7 g).

(4) The resulting insoluble fraction was added back to the '*copolymer residue*' obtained from the distillation ; and 55.5 ml of 20% HCl was added. The acid mixture, thus obtained, was subjected to vigorous reflux for a duration of 2 hours. The silicon oils were carefully washed with distilled water until it became neutral.

The yield of the desired product, *simethicone*, was 142 g (96.66% of the theoretical yield).

4.8.36.6 Precautions

(1) The addition of 0.75 g NaOH in Step (2) is extremely important and vital to augment the formation of straight chain polymers.

(2) The distillation of alcohol in Step (3) should be carried out until the temperature reaches 100°C.

4.8.36.7 Physical Parameters. Simethicone is obtained as clear colourless liquids. It has been observed that its viscosity enhances with the extent of polymerization. It is found to be immiscible with water and alcohol ; and miscible with chloroform and ether.

4.8.36.8 Uses

(1) It is frequently used to relieve flatulence and abdominal discomfort due to the formation of excess gastro-intestinal gas.

(2) It is usually employed for several gastro-intestinal disorders along with an '*antacid*'.

(3) It is also used as a defoaming agent in '*radiography*' or '*endoscopy**' of the gastro intestinal tract (GIT).

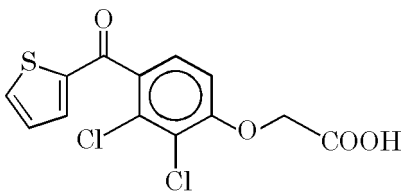
4.8.36.9 Questions for *Viva-Voce*

(1) Why is it necessary to use freshly distilled reactants in this synthesis ?

(2) Why do we add sodium hydroxide in the synthesis of simethicone ? Explain.

4.8.37 Ticrynafen

4.8.37.1 Chemical Structure

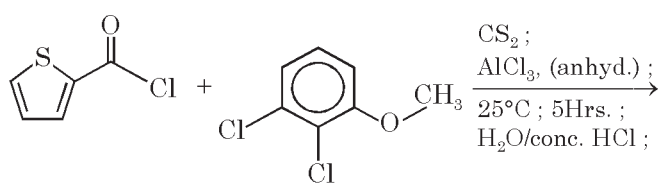


Ticrynafen

4.8.37.2 Synonyms. [2, 3-Dichloro-4-(2-thienylcarbonyl)-phenoxy] acetic acid ; [2, 3-Dichloro-4-(2-thiophencarbonyl) phenoxy]-acetic acid ; Tienilic acid ; Thienylic acid.

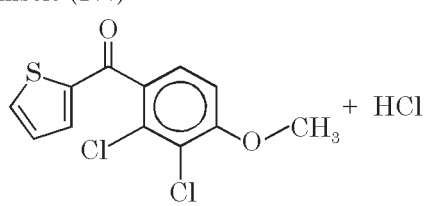
4.8.37.3 Theory

(*a*)



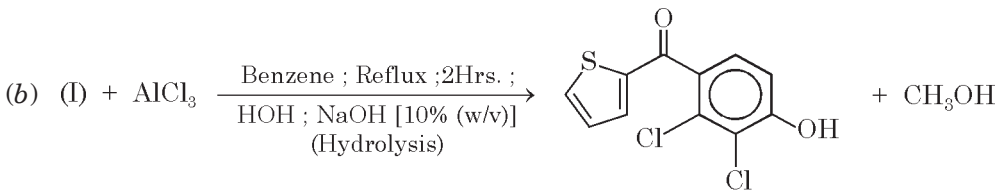
Thiophene-2-carboxylic acid chloride (156.5)

2, 3-Dichloro-anisole (177)

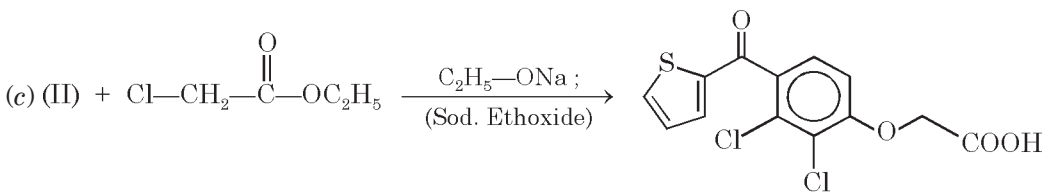


[2, 3-Dichloro-4-(2-Thiophen-carbonyl)phenoxy] -methyl—; (I) (288)

*The inspection of body organs or cavities by use of an *endoscope* (*i.e.,* a device consisting of a tube and optical system for observing the inside of a hollow organs).



2, 3-Dichloro-4-(2-thiophen carbonyl) phenol (II) (274)



Ethyl-chloro-acetate —NaCl Ticrynafen (III) (331.18)

The synthesis of *ticrynafen* may be accomplished in *three* steps as described below :

Eqn. (*a*) shows the interaction between thiophene-2-carboxylic acid chloride and 2, 3-dichloro-anisole in the presence of CS_2, anhydrous aluminium chloride ; and subsequent hydrolysis yields [2, 3-dichloro-4-(2-thiophen carbonyl) phenoxy]-methyl ; (I). The methoxy function present in the latter reactant, being an *ortho*- and *para*-director, helps to hook on the thiophene-2-carbonyl moiety at the *para*-position of the 2, 3-dichloro anisole to give (I). Obviously, the *ortho*-position is pre-occupied by a *chloro* group.

Eqn. (*b*) depicts the hydrolysis of compound (I) in the presence of aluminium chloride and benzene followed by refluxing for two hours ; and subsequently carrying out the hydrolysis with sodium hydroxide solution to give a corresponding phenol (II) *i.e.,* 2, 3-dichloro-4-(2-thiophen carbonyl)-phenol plus one mole of methanol gets eliminated.

Eqn. (*c*) illustrates the interaction of the resulting phenol (II), obtained in the previous Step (*b*), with ethyl chloro acetate in the presence of freshly prepared sodium ethoxide to give rise to the formation of the desired product, *ticrynafen*, with the elimination of sodium chloride.

4.8.37.4 Chemicals Required. 2, 3-Dichloro anisole : 55 g ; Thiophene-2-carboxylic acid chloride : 91 g ; Carbon disulphide : 180 ml ; Aluminium trichloride (anhydrous) : 210 g ; Conc. HCl (12 M) : 60 ml ; NaOH [30% (w/v)] : q.s. ; Ethanol [95% (v/v)] : q.s. ; [2, 3-Dichloro-4-(2-thiophen-carbonyl) phenoxy] methyl-, (I) : 88.6 g ; Benzene : 300 ml ; NaOH [10% (w/v)] : q.s. ; Ethanol [50% (v/v)] : q.s. ; Sodium Ethoxide (prepared by dissolving 3.45 g Na-metal in 300 ml Absolute Ethanol) : q.s. ; 2, 3-Dichloro-4-(2-thiophen carbonyl)-phenol (II) : 31 g ; Ethyl chloroacetate : 25.8 g ; Isopropanol : q.s. ;

4.8.37.5 Procedure. Ticrynafen may be prepared by carrying out the following **three** steps in a sequential manner :

Step I. Preparation of [2, 3-Dichloro-4-(2-thiophen carbonyl)-phenoxy]-methyl ; (I) :

(1) To a solution of 55 g (0.31 mol) 2, 3-dichloroanisole, 91 g (0.62 mol) thiophene-2-carboxylic acid chloride and 180 ml redistilled carbon disulphide (CS_2) in a 1 L round bottom flask ; there was introduced in small lots at intervals 82.7 g anhydrous aluminium chloride while maintaining the temperature at 23 ± 2°C. The reaction mixture was stirred at room temperature, with a mechanical agitator for 5 hours, left as such overnight, and subsequently heated for 60 minutes at 55°C carefully.

(2) The resulting reaction mixture was allowed to cool and hydrolyzed by adding 250 g crushed ice followed by 60 ml concentrated hydrochloric acid (12 M). The precipitate thus obtained is treated with NaOH solution (30%), and washed with spray of water in a Büchner funnel under suction.

The crude product is recrystallized in 95% ethanol, gave a pure product (I) weighing 88.6 g (yield 92%) having mp 108°C.

Step II. Preparation of 2, 3-dichloro-4-(2-thiophen carbonyl)-phenol (II)

(1) 88.6 g of pure product (I) obtained from step I (0.308 mol) was duly dissolved in 300 ml benzene. To this solution was added 123.5 g anhydrous aluminium chloride in small proportions at intervals, and the resulting mixture was boiled gently under reflux for a duration of 2 hours.

(2) The reaction mixture was cooled and subjected to hydrolysis by adding 500 g ice. The precipitate thus obtained was extracted and taken up in requisite quantity of 10% aqueous NaOH solution. The benzene-layer obtained after hydrolysis is concentrated under vacuo. The residual oil obtained is treated as above and the precipitate thus obtained added to the previous lot.

The crude mixture of the two precipitates is recrystallized from 50% ethanol to obtain pure product (II), 60 g having mp 142°C.

Note. The above reaction may also be effected with excellent yields in methylene chloride (CH_2Cl_2).

Step III. Preparation of Ticrynafen (III)

(1) A solution of sodium ethoxide was freshly prepared by dissolving 3.45 g sodium metal (0.15 mol) in 300 ml absolute ethanol. To this was added 31 g of product (II) (0.15 mol), obtained from Step II, and then 25.8 g ethyl chloroacetate. The resulting mixture was subjected to vigorous reflux (using a double-surface condenser) for a span of 15 hours at a stretch. Hot extraction was performed successively to eliminate the sodium chloride completely, which was obtained as a product of reaction [see Eqn. (*c*) under section 4.8.37.3].

(2) The ester precipitated on cooling the filtrate. The product was duly recrystallized in isopropanol to yield 29.4 g crystals melting at 58°C. (*The pure product melts at 63°-64°C*).

(3) The ester was dissolved in a solution of 500 ml ethanol (95%) and 9 ml NaOH solution (10 N). The resulting mixture was boiled under reflux for 30 minutes. The precipitate of the sodium salt of the acid (*i.e.,* product-III) that formed in the cold was extracted ; and subsequently taken up in warm water. The '*free acid*' *i.e.,* **ticrynafen**, was precipitated in mineral acid medium.

The crude product, *ticrynafen*, is recrystallized from 50% ethanol to give 25 g pure product having mp ranging between 148°–149°C.

4.8.37.6 Precautions

(1) In both Steps (I) and (II), the hydrolysis is performed at cold conditions using crushed ice in acidic and alkaline medium respectively.

(2) All solvents used in the synthesis *e.g.,* carbon disulphide, benzene and ethanol should be absolutely dry and freshly redistilled.

(3) It is almost necessary to obtain and recrystallize the products (*i.e.,* intermediates) (I) and (II) before proceeding to the next step so as to ensure better yield and purer final product (III).

4.8.37.7 Theoretical Yield/Practical Yield. The theoretical yield of the final product (Step III) may be calculated from the equation under theory [see section 4.8.37.3 (*c*)] as given under :

274 g 2, 3-Dichloro-4-(2-thiophen carbonyl) phenol on treatment with

Ethyl chloroacetate yields Ticrynafen = 331.18 g

∴ 31 g 2, 3-Dichloro-4-(2-thiophen carbonyl) phenol shall yield

Ticrynafen $= \frac{331.18}{274} \times 31 = 37.47$ g

Hence, Theoretical Yield of Ticrynafen = **37.47 g**

Reported Practical Yield = 25 g

Therefore, Percentage Practical Yield $= \frac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100$

$= \frac{25}{37.47} \times 100 =$ **66.72**

4.8.37.8 Physical Parameters

Ticrynafen is obtained as crystals from 50% ethanol having mp 148°–149°C. Its pKa value is 2.7.

4.8.37.9 Uses

(1) It is used as a diuretic.

(2) It is also employed as an uricosuric agent*.

(3) It also finds its application as an antihypertensive drug.

4.8.37.10 Questions for *Viva-Voce*

(1) How would you accomplish the synthesis of ticrynafen ?

(2) What are the various pharmacological actions of ticrynafen ?

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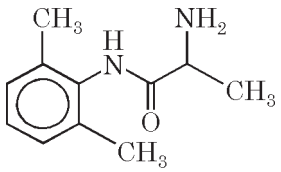
* A drug that increases the urinary excretion of uric acid, thereby reducing the concentration of uric acid in the blood. It is used to treat gout.

4.8.38 Tocainide

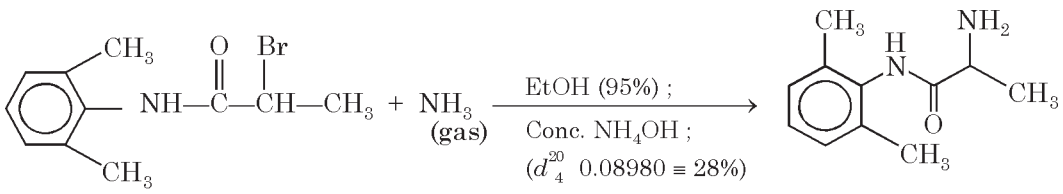
4.8.38.1 Chemical Structure



Tocainide

4.8.38.2 Synonyms. 2-Amino-N-(2, 6-dimethylphenyl) propanamide ; 2-Aminopropiono-2′, 6′-xylidide.

4.8.38.3 Theory



2-Bromo-2′,6′,-propion-oxylidide (256) —HBr ; Tocainide (192.26)

To-cainide is synthesized by the interaction of 2-bromo-2′, 6′-propionoxylidide in the presence of ethanol, concentrated liquid ammonium hydroxide and ammonia gas at room temperature when bromo group at C-2 gets replaced by an amino function to yield a mole of tocainide with the elimination of one mole of hydrogen bromide.

4.8.38.4 Chemicals Required. 2-Bromo-2′, 6′-propionoxylide : 50 g ; Ethanol [95% (v/v)] : 500 ml ; Conc. Aqueous Ammonia [d_4^{20} 0.8980] : 400 ml ; Ammonia gas : q.s. ; Hydrochloric Acid (3 M) : 80 ml ; Sodium Hydroxide solution (7 M) : 50 ml ; Methylene chloride (CH_2Cl_2) : 100 ml ; Anhydrous Potassium Carbonate : q.s. ; Chloroform : 300 ml ; Dry Hydrogen chloride gas : q.s. ;

4.8.38.5 Procedure. The various steps involved in the synthesis of tocainide are as stated under :

(1) A suspension of 50 g (0.195 mol) 2-bromo-2′, 6′-propiono-xylidide in a mixture of 500 ml ethanol (95%) and 400 ml concentrated aqueous ammonia was adequately saturated with gaseous ammonia by bubbling it through the medium at room temperature in a 2 L round bottom flask in an efficient fuming cupboard. The saturation with NH_3^- gas performed under constant mechanical stirring. After a duration of 25 hours the mixture was resaturated with NH_3-gas. The total period of stirring at an ambient temperature should be upto 116 hours. A sample withdrawn at this material time was subjected to analysis by a previously set '**gas-chromatographic**' assembly which gave an indication that almost 95% of the bromo compound had been duly converted into the desired product, *tocainide*.

(2) The solvents were removed under vacuum, and the residue was taken up in 80 ml of 3 M hydrochloric acid. After addition of 220 ml water, the insoluble component was

filtered off in a Büchner funnel under suction, washed thoroughly with a spray of 100 ml water, and dried subsequently. The insoluble substance weighed 9.5 g and was chiefly the '*unreacted bromo compound*'.

(3) The clear filtrate was treated with 50 ml sodium hydroxide solution (7 M), extracted thrice with pure redistilled methylene chloride (CH_2Cl_2) *i.e.,* 50 ml + 2 × 25 ml portions, dried over anhydrous potassium carbonate, and subsequently evaporated under vacuo.

The yield of the crude product was 26.8 g and obtained as a colourless solidifying oil.

4.8.38.6 Precautions

(1) The agitation of the reactants at room temperature must be continued upto 116 hours in Step (1).

(2) The '**unreacted bromo compound**' should be removed from the reaction mixture before proceeding to the recovery of the desired compound *i.e. ; tocainide*.

4.8.38.7 Recrystallization. The crude product, 26.8 g, was dissolved in 200 ml chloroform. Dry hydrogen chloride gas was made to bubble through the resulting solution till such time when a small test sample (TS) of the solution gave a positive acid test to a wet pH indicator paper. The precipitate thus obtained was recovered by filtration under suction, washed with chloroform and dried under vacuum to obtain a crystalline product having mp 246°-247.5°C.

4.8.38.8 Theoretical Yield/Practical Yield. The theoretical yield may be calculated from the equation given under theory (section 4.8.38.3) as stated below :

256 g 2-Bromo-2′, 6′-propionoxylidide on vigorous amination yields, Tocainide = 192.26 g

∴ 50 g 2-Bromo-2′, 6′-propionoxylidide shall yield Tocainide $= \frac{192.26}{256} \times 50 = 37.55$ g

Hence, Theoretical Yield of Tocainide = **37.55 g**

Reported Practical Yield = 26.8 g

Therefore, Percentage Practice Yield $= \frac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100$

$= \frac{26.8}{37.55} \times 100 =$ **71.37**

4.8.38.9 Physical Parameters. The physical parameters of the (±)-Tocainide hydrochloride, $C_{11}H_{16}N_2O.HCl$, obtained as crystals from a mixture of ethanol/ether, have mp ranging between 246-247°C.

4.8.38.10 Uses

(1) It is a 'lidocaine' analoque invariably employed in treating ventricular arrythmias.

(2) It belongs to the **class 1 B**-antiarrythmic drugs.

4.8.38.11 Questions for *Viva-Voce*

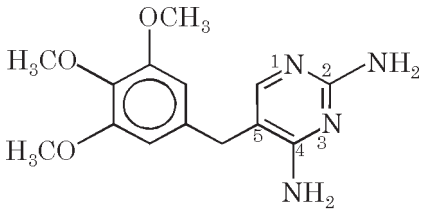
(1) How would you remove the 'unreacted bromo compound' from the reaction mixture ?

(2) Why is it recommended to carry out the amination reaction at room temperature for a total span of 116 hrs ?

(3) How would you ascertain that 95% of the '*bromo compound*' has been duly converted into the desired product *i.e.,* **tocainide** ?

4.8.39 Trimethoprim

4.8.39.1 Chemical Structure

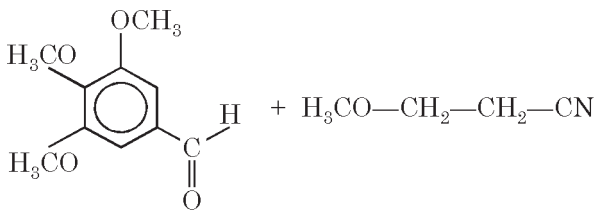


Trimethoprim

4.8.39.2 Synonym. 5-[(3, 4, 5-Trimethoxyphenyl) methyl]-2, 4-pyrimidinediamine ; 2, 4-Diamino-5-(3, 4, 5-trimethoxybenzyl) pyrimidine ;

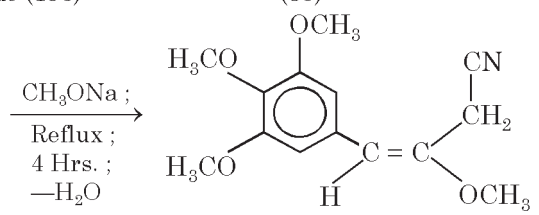
4.8.39.3 Theory

(*a*)



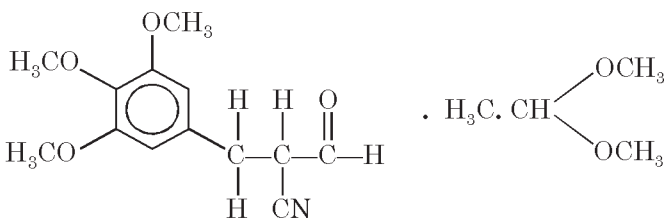
3, 4, 5-Trimethoxy-benzaldehyde (196)

β-Methoxypropionitrile (85)

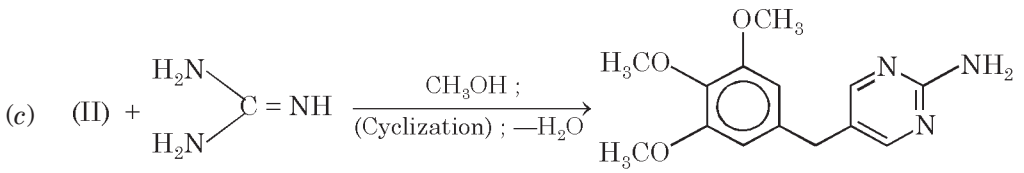


3, 4, 5-Trimethoxy-2′-methoxymethyl cinnamonitrile (262) (I)

(*b*) (I)



3, 4, 5-Trimethoxy-2′-cyano-dihydro-cinnamaldehyde dimethyl acetal (291) (II)



Guanidine (59.07) Trimethoprim (III) (290.32)

The synthesis of *trimethoprim* involves **three** different steps as given below :

Eqn. (*a*) : shows the interaction of 3, 4, 5-trimethoxy benzaldehyde with β-methoxypropionitrile in the presence of sodium methoxide to yield 3, 4, 5-trimethoxy-2′-methoxymethyl cinnamonitrile (I) with the elimination of a mole of water.

Eqn. (*b*) : illustrates the treatment of the intermediate (I) with freshly prepared sodium methoxide under reflux for 24 hours to give rise to the formation of an acetal adduct 3, 4, 5-trimethoxy-2′-cyano-dihydroxcinnamaldehyde dimethyl acetal (II).

Eqn. (*c*) : shows the cyclization of intermediate (II) with guanidine, in methanol, to yield the desired product, *trimethoprim,* (III) with the elimination of water.

4.8.39.4. Chemicals Required. Pure freshly cut sodium metal : 16 g ; Methanol (Absolute) : 1.5 L ; β-Methoxypropionitrile : 47.5 g ; 3, 4, 5-Trimethoxybenzaldehyde : 98 g ; 3, 4, 5-Trimethoxy-2′-methoxymethylcinnamonitrile (I) : 106 g ; Benzene : 800 ml ; 3, 4, 5-Trimethoxy-2′-cyanodihydro-cinnamaldehyde dimethyl acetal (II) : 31.5 g ; Guanidine : 1.48 g ; 2, 4-Diamino-5-(3, 4, 5-Trimethoxybenzyl) pyrimidine (III) : 28 g ; H_2SO_4 (Aq. soln.) (3N) : 70 ml ; NaOH soln. [50% (w/v)] : 50 ml ;

4.8.39.5. Procedure. The synthesis of *trimethoprim* may be accomplished in **three** steps as described sequentially under :

Step I. Preparation of 3, 4, 5-Trimethoxy-2′-methoxymethyl-cinnamonitrile (I) :

(1) 6 g (0.26 mol) Freshly cut piece of sodium metal was dissolved in 300 ml methanol under gentle stirring and refluxing. When most of the Na-metal dissolved (to form sodium methoxide), introduce carefully into the 1 L round bottom flask 47.5 g (0.55 mol) β-methoxypropionitrile and 98 g (0.5 mol) 3, 4, 5-trimethoxybenzaldehyde ; and the reaction mixture was refluxed gently for a period of 4 hours. The resulting mixture was cooled first to the ambient temperature and then chilled in an ice-bath with the addition of 150 ml water into reaction flask. The product crystallized rapidly. The crystallization was premitted to proceed at 5°-10°C under gentle stirring for 60-70 minutes. The crystallized product was separated in a Büchner funnel under suction and washed on the filter paper with 200 ml of 60% (v/v) ice-cold methanol. The crude material (I) was air-dried, and may be used for the subsequent steps without any purification. Its yield was 93.5 g having mp 78°-80°C.

(*a*) **Recrystallization.** A pure sample, recrystallized from methanol, melted at 82°C. The yield of 3, 4, 5-trimethoxy-2′-methoxymethyl cinnamonitrile (I) was found to be 92 g.

(*b*) **Theoretical Yield/Practical Yield.** The theoretical yield may be calculated from the equation under theory [section 4.8.39.3 (*a*)] as given below :

196 g 3, 4, 5-Trimethoxybenzaldehyde on interaction with
β-Methoxy-propionitrile shall yield = 262 g

∴ 98 g 3, 4, 5-Trimethoxybenzaldehyde shall
yield Product (I) $= \frac{262}{196} \times 98 = 131$ g

Hence, Theoretical Yield of Product (I) = **131 g**

Reported Practical Yield = 93.5 g

Therefore, Percentage Practical Yield $= \frac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100$

$= \frac{93.5}{131} \times 100 =$ **71.37**

Step II. Preparation of 3, 4, 5-Trimethoxy-2′-cyano-dihydrocinnamaldehyde dimethyl acetal (II) :

(1) 19 g (0.83 mol) freshly cut piece of sodium metal was dissolved in 300 ml absolute methanol, 106 g of product (I), obtained in Step I, was added into a 1 L dry round bottom flask fitted with a double-surface reflux condenser. The reaction mixture was gently refluxed for 24 hours. The solution, which had turned almost brown, was poured carefully into 1 L of distilled water. The precipitated oily residue was successively extracted with benzene. The combined benzene layer (~ 600 ml) were washed thoroughly *three times* with approximately 550 ml water. The benzene was removed by distillation under reduced pressure on an electric water bath.

(2) The residual brown oil thus obtained was subjected to distillation under vacuo, bp 215°-225°C/11 mm. The clear, viscous oil 3, 4, 5-trimethoxy-2′-cyano-dihydro-cinnamaldehyde (II), weighed 83.2 g. It has a n_D^{23} = 1.5230. It became solid upon standing.

(*a*) **Recrystallization.** The crude product was recrystallized from methanol and melted at 69°-70°C. It exhibited a sharp mp and n_D^{25} = 1.5190.

(*b*) **Theoretical Yield/Practical Yield.** The theoretical yield is calculated from the equation under theory [section 4.8.39.3 (*b*)] as stated below :

262 g of (I) on being treated with Sodium Methoxide under reflux yields 3, 4,
5-Trimethoxy-2′-cyano-dihydro-cinnamaldehyde
dimethyl acetal (II) = 291 g

∴ 106 g of (I) shall yield Product (II) $= \frac{291}{262} \times 106 = 117.73$ g

Hence, Theoretical Yield of Product (II) = **117.73 g**

Reported Practical Yield = 83.2 g

Therefore, Percentage Practical Yield $= \frac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100$

$= \frac{83.2}{117.73} \times 100 =$ **70.67**

Step III. Preparation of Trimethoprim (III) :

(1) 31.5 g (0.107 mol) of Product (II), obtained from Step II, 1.48 g guanidine were dissolved in 200 ml absolute methanol in a 1 L dry RB-flask ; and the contents were refluxed for 2 hours at a stretch. The methanol was distilled off completely under gentle stirring in an electeic water bath maintained between 110°-120°C. A yellowish crystalline mass was obtained as a residue which solidified almost completely.

(2) After allowing it to cool, the resulting residue was duly slurried with 100 ml distilled water, collected in a Büchner funnel under suction and dried subsequently under vacuo.

The yield of the crude product, trimethoprim (III), amounted to 28.3 g, having mp 199°-200°C, and had a distinct yellowish tinge.

(*a*) **Recrystallization.** 20 g of the above crude product (III) was added to 30 ml aqueous H_2SO_4 (3 N) at 60°C under gentle stirring. The solution was subsequently chilled to 5°-10°C under stirring. The crystalline sulphate of the product was duly collected by vacuum filtration and washed on the filter *twice* with 10 ml of chilled 3 N aqueous H_2SO_4 each time.

Note. *1.3 g (6.5%) of discoloured material was duly recovered from the above filtrate, which showed mp 195°-196° ; and this was reserved to be added on to the subsequent lots for purification.*

The resulting sulphate of product (III) was duly dissolved in 200 ml of hot DW, activated charcoal powder added and filtered. The desired purified product was precipitated from the clear colourless filtrate by the gradual addition of a solution of 20 g NaOH dissolved in 40 ml DW under thorough chilling. The resulting precipitate, thus obtained, was filtered by suction and washed thoroughly with water on the filter paper. The white pure product (III) was obtained to the extent of 17.5 g (88%) having mp 200°-201°C.

(*b*) **Theoretical Yield/Practical Yield.** The theoretical yield of Trimethoprim (Product III) may be calculated from the equation under theory [section 4.8.39.3 (*c*)] as stated under :

291 g of (II) on reaction with Guanidine forms Trimethoprim = 290.32 g

$\therefore$ 31.5 g of (II) shall yield Trimethoprim $= \dfrac{290.32}{291} \times 31.5 = 31.43$ g

Hence, Theoretical Yield of Trimethoprim = **31.43 g**

Reported Practical Yield = 28.3 g

Therefore, Percentage Practical Yield $= \dfrac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100$

$= \dfrac{28.3}{31.43} \times 100 =$ **90.04**

4.8.39.6 Precautions

(1) All steps described explicitely under the **three different products** should be observed rigidly.

(2) Sodium methoxide used in Step I and II must always be prepared afresh from freshly cut sodium metal and absolute methanol in a perfectly dry condition.

4.8.39.7 Physical Parameters. Trimethoprim is obtained as a white to cream, bitter crystalline powder, mp 199°-203°C. Its solubility in g/100 ml at 25°C : N, N-Dimethylacetamide (DMAC) 13.86 ; Benzyl alcohol : 7.29 ; Propylene glycol : 2.57 ; Chloroform : 1.82 ; Methanol : 1.21 ; Water : 0.04 ; Solvent Ether : 0.003 ; and Benzene : 0.002. It has pKa value 6.6.

4.8.39.8 Uses

(1) Its most important use is as an antibacterial agent against a wide spectrum of organisms, such as : *Streptococcus pyrogenes, viridans* and *pneumoniae ; Staphylococcus aureus* and *epidermidis, H. influenzae, Klebsiella-Enterobacter-Serratia, E. coli*, various *Shigella* and *Salmonella, Bordetella pertussis, Vibrio cholerae* and *Plasmodia*.

(2) It is used widely in combination with **sulphamethoxazole**.

(3) The combination of *dapsone* and *trimethoprim* is used in the treatment of leprosy and imfectious caused by *Mycobactrium avium*.

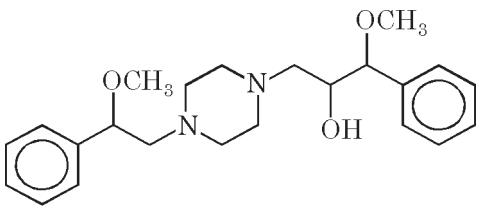
4.8.39.9 Questions for *Viva-Voce*

(1) How would you accomplish the synthesis of '**trimethoprim**' from 3, 4, 5-trimethoxy benzaldehyde ? Explain.

(2) What are the various therapeutic applications of '**Trimethoprim**' ?

4.8.40 Zipeprol

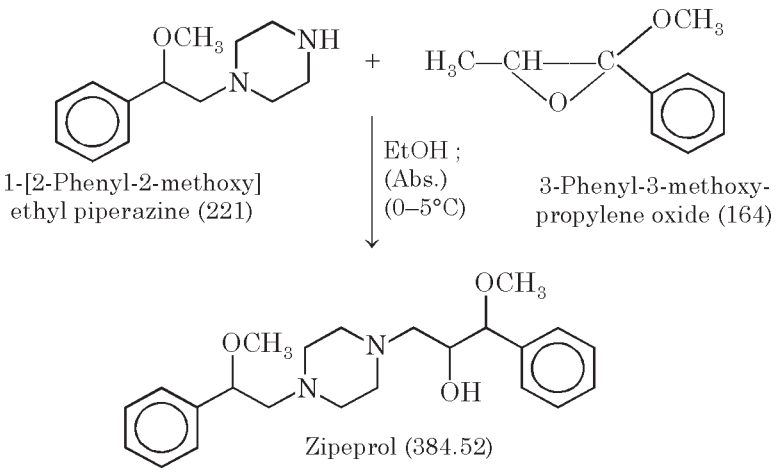
4.8.40.1 Chemical Structure



Zipeprol

4.8.40.2 Synonyms. 4-(2-Methoxy-2-phenylethyl)-α-(methoxyphenyl-methyl)-1-piperazeneethanol ; 1-(2-Methoxy-2-phenylethyl)-4-(2-hydroxy-3-methoxy-3-phenylpropyl) piperazine.

4.8.40.3 Theory



The interaction between 1-[2-phenyl-2-methoxy] ethyl piperazine and 3-phenyl-3-methoxy propylene oxide in the presence of absolute ethanol at a temperature between 0-5°C gives rise to the formation of zipeprol. The reaction proceeds with the cleavage of epoxide ring to get converted to a secondary alcohol.

4.8.40.4 Chemicals Required. 1-[2-Phenyl-2-methoxy] ethyl piperazine : 393 g (1.78 mol) ; 3-Phenyl-3-methoxy propylene oxide : 22 g (0.134 mol) ; Absolute Ethanol : 1250 ml.

4.8.40.5 Procedure. The various steps involved in the synthesis of **zipeprol** are as enumerated below :

(1) In a reactor (2 L-capacity) adequately fitted with a mechanical stirrer, a reflux refrigerant and a thermometer, there is transferred : 393 g (1.78 mol) 1-[2-phenyl-2-methoxy] ethyl piperazine and 22 g (0.134 mol) 3-phenyl-3-methoxy propylene oxide in 750 ml absolute ethanol.

(2) When the slightly exothermic reaction has almost ceased, thereby raising the temperature to about 20°C, then subsequent heating is effected upto 60°C for a duration of 90-100 minutes.

(3) The resulting reaction mixture is initially cooled to room temperature, and then further chilled to 4°C in a freezing mixture or ice-bath. The product was left to crystallize for 12-14 hours (at 4°C). The crude product, thus obtained is filtered in a Büchner funnel under suction to obtain 428 g having mp 81°-82.5°C.

4.8.40.6 Precautions

(1) The first step of the reaction is exothermic in nature, therefore, every care should be taken not to allow the temperature of the reaction mixture beyond 20°C. Besides, close monitoring the use of reflux refrigerant are extremely important.

(2) Once the reaction ceases to evolve heat, the reaction mixture must be further heated upto 60°C for the stipulated period 80 as to complete the reaction.

4.8.40.7 Recrystallization. The crude product is recrystallized in 500 ml of absolute ethanol to obtain white crystalline powder (420 g) having sharp mp 83°C.

4.8.40.8 Theoretical Yield/Practical Yield. The theoretical yield may be calculated from the equation under theory (section 4.8.40.3) as stated below :

221 g 1-[2-Phenyl-2-methoxy] ethyl piperazine on interaction

with 3-Phenyl-3-methoxypropylene oxide yields Zipeprol = 384.52 g

∴ 393 g 1-[2-Phenyl-2-methoxy] ethyl piperazine

shall yield Zipeprol $= \frac{384.52}{221} \times 393 = 683$ g

Hence, Theoretical Yield of Zipeprol = **683 g**

Reported Practical Yield = 428 g

Therefore, Percentage Practical Yield $= \frac{\text{Practical Yield}}{\text{Theoretical yield}} \times 100$

$= \frac{428}{683} \times 100 =$ **62.66**

4.8.40.9 Physical Parameters. Zipeprol is obtained as white crystals from absolute ethanol having mp 83°C.

4.8.40.10 Uses

(1) It is used as a bronchodilator.

(2) It is also employed as an antitussive.

4.8.40.11 Questions for *Viva-Voce*

(1) How would you explain the formation of Zipeprol from 1-[2-phenyl-2-methoxy] ethyl piperazine and 3-phenyl-3-methoxy propylene oxide ?

(2) Why is it necessary to perform the reaction under cold conditions using reflux refrigerant ?

(3) What are the therapeutic uses of Zipeprol ?

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