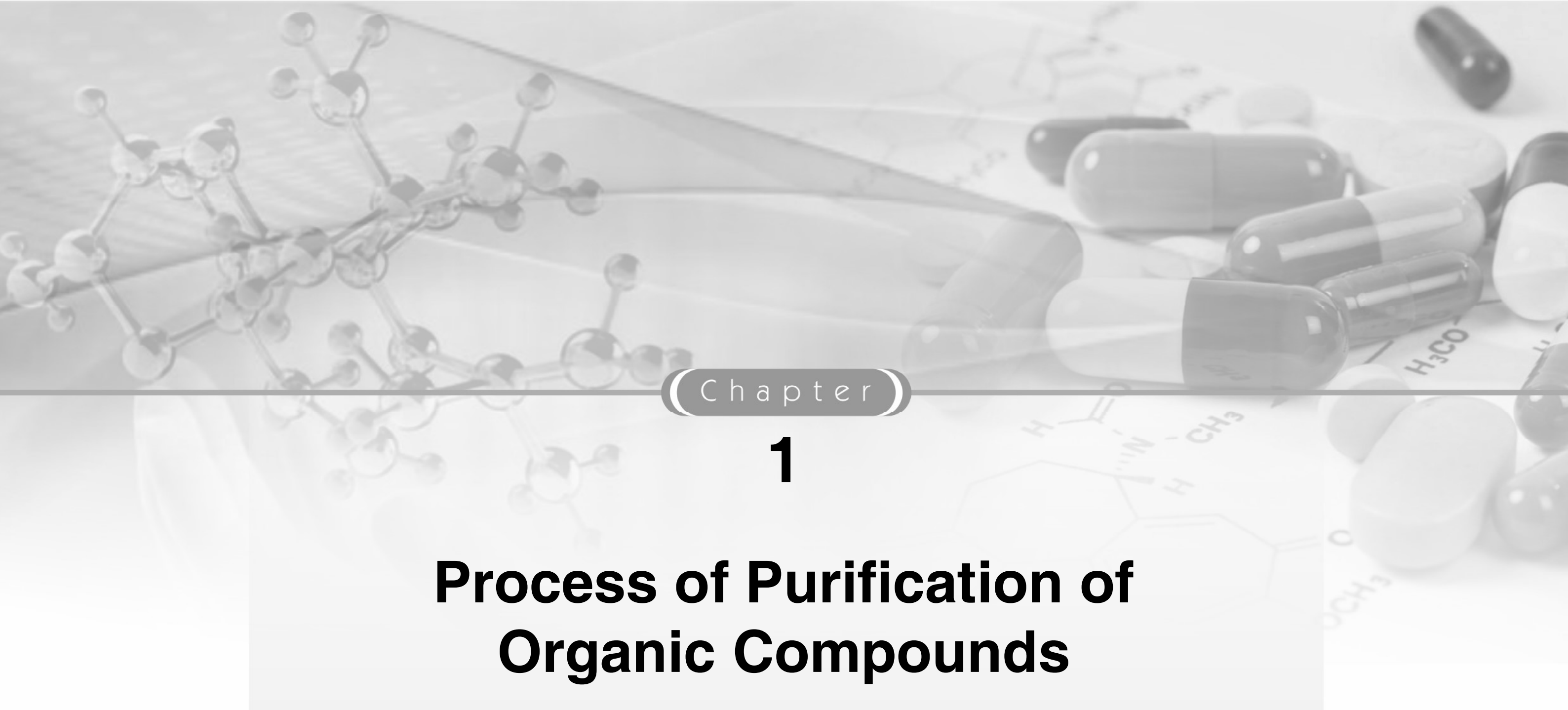
PART

I

Practical Medicinal Chemistry I

Course Code BP406P



Chapter 1

Process of Purification of Organic Compounds

Quality of the prepared organic or medicinal compounds can be confirmed by their purity and yield of the product obtained. For that the compounds used for analysis or synthesis must be pure because an impure compound will not give a sharp and correct melting point or boiling point. The purification of organic compounds is necessary, though complex, step after its extraction from a natural source or synthesis in the laboratory. An impure compound may be purified by crystallization or sublimation and impure liquids are purified by distillation process. One easy method to check the purity of an organic compound is to either melt or boil it as organic compounds tend to have sharp melting and boiling points. In general, it may be said that a pure compound has usually a sharp melting-point, whereas an impure substance has an indefinite melting-point, and will therefore melt slowly and indecisively over a range of several degrees. The method of purification of the organic compounds depends mainly on the nature of the compound and the impurities present. Purification means the removal of unwanted impurities present in an organic compound. The general methods of purification are:

- Sublimation
- Crystallization
- Distillation
- Simple distillation
- Fractional distillation
- Steam distillation
- Vacuum distillation (distillation under reduced pressure)
- Air-sensitive vacuum distillation
- Short path distillation
- Zone distillation
- Extraction
- Differential extraction
- Chromatography

METHODS OF PURIFICATION

Organic compounds are isolated from either natural sources or reaction synthetic mixtures. In natural mixtures, the target generally constitutes a low percentage proportion. In synthetic mixture, the target may be the major product, but not pure. The reaction mixture contains always impurities. In order to obtain pure organic substances, mixtures are purified by physical technics, according to their nature, especially physical state and polarity. This **purification** may follow one or more purification steps and methods.

Sublimation

Sublimation is the direct physical transformation from of a substance from solid state to gaseous one (example: Naphthalene, benzoic acid and camphor). The reverse transformation is possible it is called deposition. It is observed by when cooling the vapors, yielding pure solid crystals called sublimate.

$$\text{Solid} \underset{\text{Cool}}{\overset{\text{Heat}}{\rightleftharpoons}} \text{Vapor}$$

Some solids can directly pass to the vapour state without going through the liquid phase. The purification technique which exploits this property is called sublimation. It is helpful in separating sublimable compounds from non-sublimable ones.

It can define sublimation as the transition of a substance from the solid phase to the gaseous phase without changing into the liquid phase. This process is an endothermic phase transition that occurs at a temperature and pressure below the triple point of the substance. Desublimation or deposition is the reverse of this process in which a gas is directly converted into solid-state (Fig. 1.1).

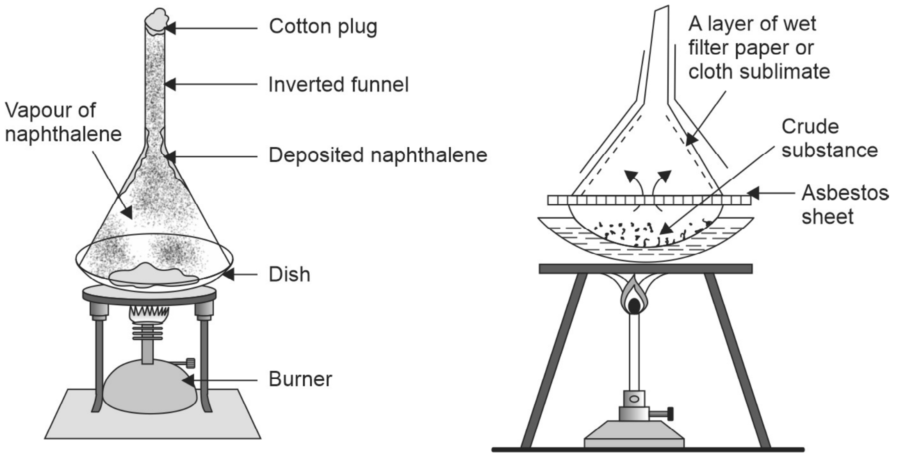


Fig. 1.1: Sublimation process

- Elements and compounds mainly possess three different states at various temperatures.
- The transition from solid state to gaseous state requires a transition of solid-state to liquid state and liquid state to a gaseous state.
- If solids possess sufficient vapour pressure at a particular temperature than they can directly sublime into the air.
- Solids which have high pressure at their triple point show sublimation.
- The triple point is the point at which the pressure and temperature of the substance are such that it can exist in all three states of matter simultaneously. The triple point is a characteristic point of a substance.

- There are various examples of sublimation which are experienced by us in our everyday life.

Examples

- The best example of sublimation is dry ice which is a frozen form of carbon dioxide. When dry ice gets exposed to air, dry ice directly changes its phase from solid-state to gaseous state which is visible as fog. Frozen carbon dioxide in its gaseous state is more stable than in its solid-state.
- Another well-known example of sublimation is naphthalene which is an organic compound. Naphthalene is usually found in pesticides such as mothball. This organic compound sublimes due to the presence of non-polar molecules that are held by van der Waals intermolecular forces. At a temperature of 176°F naphthalene sublimes to form vapours. It desublimates at cool surfaces to form needle-like crystals.

Sublimation finds practical application in forensic sciences. Dye-sublimation printers help in rendering digital pictures in a detailed and realistic fashion which helps in the analysis of substances. Chemists usually prefer sublimation as a purification method to purify volatile compounds.

Crystallization

Crystallization is the most common method for purification of solid organic compounds.

Impurities and organic compound have different solubilities in a given solvent. Crystallization is a simple, effective, and very important technique to separate and purify solids. Crystallization is used to purify a solid. It is based on the fact that all organic compounds are more soluble in hot than in cold solvents, so that solid gets dissolved on heating and is obtained back on cooling. The process requires a suitable solvent. A suitable solvent is one which readily dissolves the solid (solute) when the solvent is hot but not when it is cold. The best solvents exhibit a large difference in solubility over a reasonable range of temperatures (e.g. water can be a crystallization solvent between 0 and 100°C; hydrocarbon solvents such as hexanes or petroleum ether have a different T range since they can be cooled below 0° but boil below 100°). Crystallization can be performed using either water, a single solvent, or multiple solvents, depending upon the specific requirements of a given compound.

The principle here is that the compound and the impurities have different solubilities in a solvent. A solvent is chosen where the compound to be purified is sparingly soluble, that is, it is sparingly soluble at lower temperature and soluble at a higher temperature. The solution is heated to get a saturated solution, and on cooling, the crystals of the compounds are removed via filtration.

For example, crystals of benzoic acid can be crystallized with water. Benzoic acid is sparingly soluble in cold water and soluble in hot water.

If the mixture contains impurities that have the same solubility as of the compound to be purified, repeated crystallization is performed.

Crystallization can be defined as the process through which the atoms/molecules of a substance arrange themselves in a well-defined three-dimensional lattice and consequently, minimize the overall energy of the system. When a substance is subjected to crystallization, its atoms or molecules bind together through well-defined angles.

On adding a solid substance in a liquid and stirring it, the solid dissolves in the fluid. But when added more and more solid to the liquid, a point comes after which no more solid dissolves in the liquid. This point is called a saturation point and the fluid is called a saturation solution.

Steps Involved in Crystallization

The following steps are involved in the purification by crystallization:

- Selection of a solvent
- Dissolution of the sample
- Decolourisation of the solution
- Hot filtration
- Cooling for crystallization
- Cold filtration
- Washing the crystals
- Drying the crystals
- Checking the purity
- Melting point determination
- Boiling point fetermination and distillation

Common Solvents for Crystallization

Common solvents for crystallisation are acetone, chloroform, carbon tetrachloride, water, petroleum ether, diethylether, ethanol, benzene, cyclohexane, acetic acid, etc.

Characteristics of a solvent:

a. Chosen for solubilizing power—solubility usually increases with increasing Time
b. Polarity is important like polar compounds are more soluble in polar solvents; nonpolar compounds in nonpolar solvents
c. Should be inert but few are, e.g, acetic acid is sometimes used as a solvent although it will certainly react with basic compounds
d. Almost all solvents are **combustible:** Avoid flames
e. Mixed solvents (e.g. 1:1 water/methanol) provide a huge range of possible solvents but they must be soluble in one another.

In certain cases, recrystallization may be used for the separation of a solid mixture. When the impure solid is dissolved in a minimum volume of a suitable hot solvent and the resulting solution is gradually cooled, saturation and eventual crystallization of the pure compound occurs. Impurities in a solid are of two kinds—soluble and insoluble and recrystallization involves the removal of both to purify a solid. Insoluble impurities are first removed by gravity filtration of the hot solution while the soluble impurities remain dissolved in the cold saturated solution (*mother liquor*) after precipitation of the desired compound. The pure crystals are separated from the supernatant liquid by suction filtration. After drying, the purity is checked by a melting point determination.

Filtration

Filtration is used whenever an insoluble solid is to be separated from a liquid. Simple gravity filtration (usually hot filtration) is employed to remove insoluble solid impurities from a liquid, while suction filtration (usually cold filtration) is used to collect a desired solid or crystalline product.

Preparation of a fluted filter paper for filtration: The filter paper is first divided into eight equal sectors by making fourfold in the paper. The folding is continued, the edge 2,1 is then folded on to 2,6 and 2,3 to 2,5 to produce new folds 2,7 and 2,8 respectively. further 2,3 to 2,6 and 2,1 to 2,5 give new folds 2,9 and 2,10 respectively. Finally, a fold is made on each of the eight segments, e.g. between 2,3 and 2,9/2,9 and 2,6 and so on in a direction opposite to the first series of folds to give a fan arrangement which on opening gives a fluted filter paper. The above sequence is shown in Fig. 1.2.

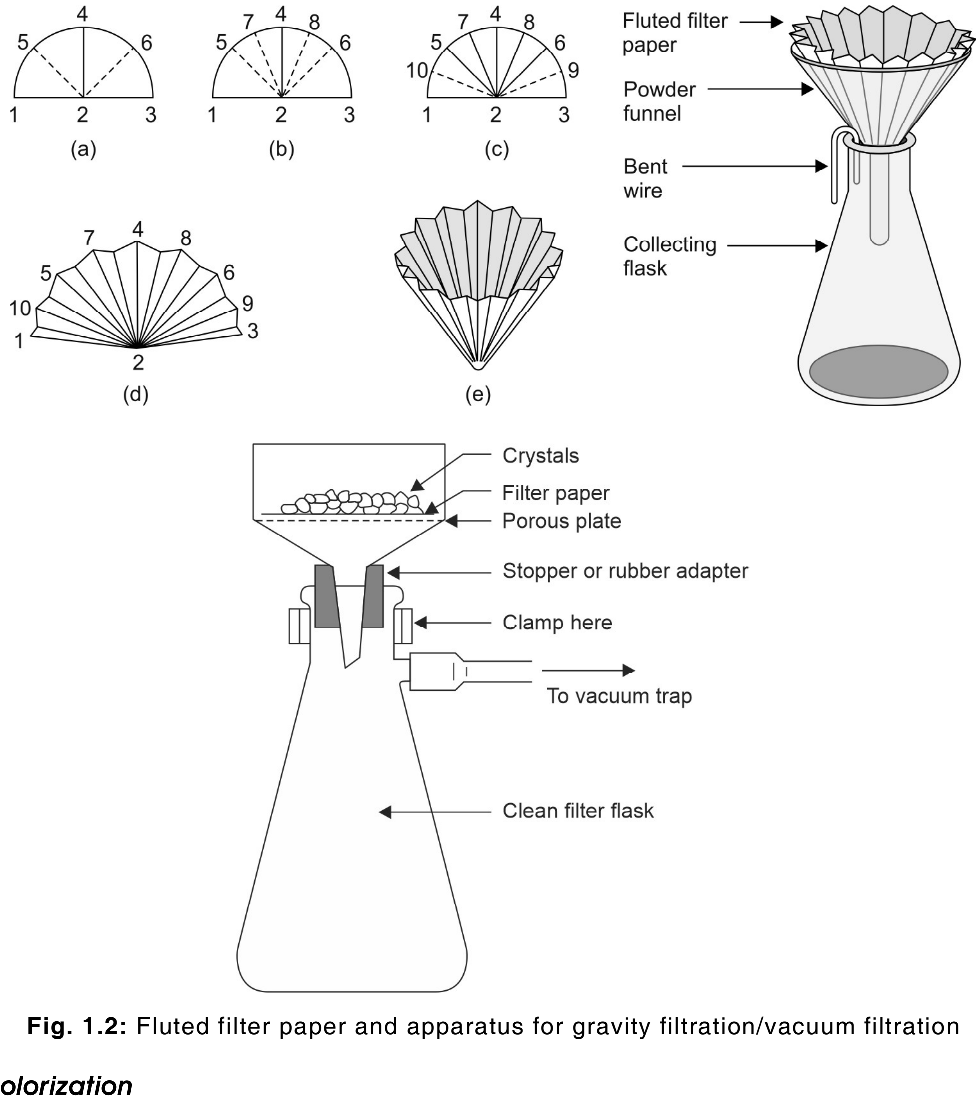


Fig. 1.2: Fluted filter paper and apparatus for gravity filtration/vacuum filtration

Decolorization

Most organic compounds are colorless. Highly conjugated compounds (e.g. polar polymers) will absorb light in the visible region of the spectrum and thus be 'colored'. If these highly polar, large molecules are impurities, they can be removed by use of finely granulated activated charcoal. Polar compounds (e.g. polar impurities) adsorb to the charcoal which is insoluble in the solvent and can be filtered away from solution. Decolorization is used for the removal of colored impurities from a solution. This is achieved by the addition of activated charcoal to the solution and mixing thoroughly. If charcoal is added to a cold solution, the solution is first brought to a boil before hot filtration. When however, it is added to a hot solution, the flask should be removed from the heat source before the addition, otherwise bumping will occur. Charcoal is finally removed by filtration leaving an almost colorless solution.

Drying

The process of drying, if applied to a solid substance is aimed to remove residual solvent (organic or water) adhering to the solid particles/crystals. This is usually done by air drying (spreading over a sheet of paper/filter paper) and/or heating in an oven to enhance evaporation of the solvent. Drying of an organic liquid, however, involves the removal of traces of water (moisture) using chemical drying agents. Such cases are encountered in extraction where the organic phase is in direct contact with the aqueous phase. After separating the layers, traces of water in the organic phase are removed by the addition of a suitable drying agent. Some common examples are—calcium chloride, magnesium sulfate, sodium sulfate, sodium hydroxide and potassium hydroxide.

Crystallization Process (Fig. 1.3)

1. The solution is heated in an open container
2. The solvent molecules start evaporating, leaving behind the solutes
3. When the solution cools, crystals of solute start accumulating on the surface of the solution
4. Crystals are collected and dried as per the product requirement
5. The undissolved solids in the liquid are separated by the process of filtration

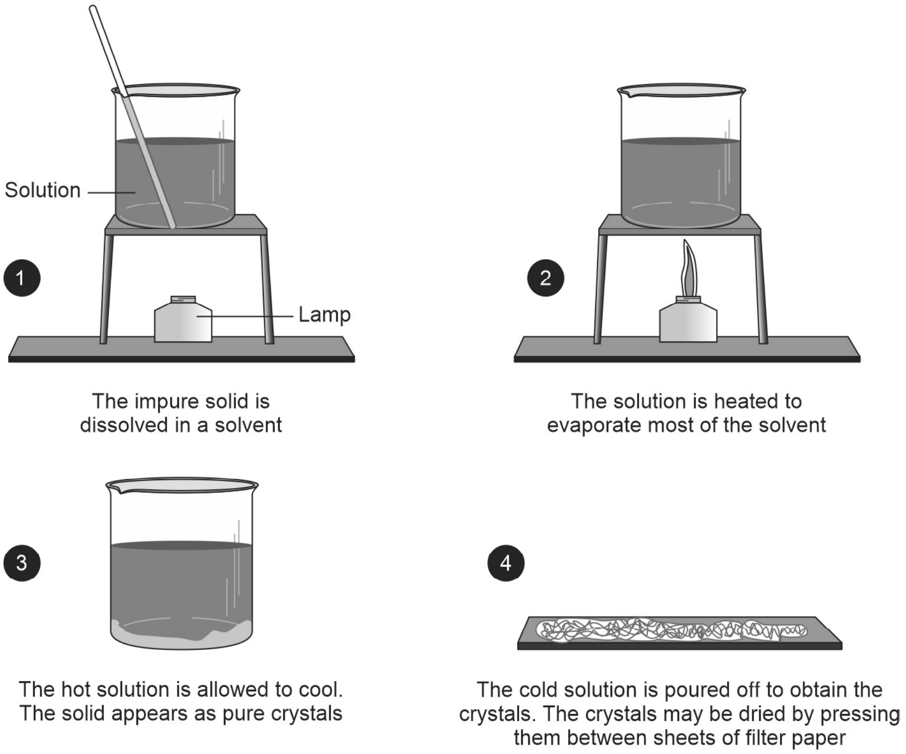


Fig. 1.3: Crystallization process

6. The size of crystals formed during this process depends on the cooling rate
7. Many tiny crystals are formed if the solution is cooled at a fast rate
8. Large crystals are formed at slow cooling rates.

Melting Point Determination (Fig. 1.4)

The melting point of a solid is the temperature at which transition from solid to liquid occurs at atmospheric pressure; or the temperature at which solid and liquid phases are in equilibrium at a pressure of one atmosphere. A simple device for determining melting points is used and it consists of a thermometer fitted through a cork and suspended into a long-necked flask which is three quarters filled with a high boiling and stable liquid like paraffin oil, di-butylphthalate or silicon oil. The thermometer bulb should be about 1 cm above the bottom of the flask. The sample in the capillary tube is fastened to the thermometer with a rubber band placed above the level of the oil. The capillary tube should be close to and on a level with the thermometer bulb. To determine the melting point of a solid, a small amount of the powdered substance is introduced into a capillary tube which is then attached to a thermometer and placed in the oil bath. The bath is heated rapidly to within 20°C of the expected melting point then slowly, and at a constant rate of 2–3° per minute, close to the melting point. The temperature at which the solid begins to melt, and that at which it is completely liquid, is recorded as the melting point range of that substance.

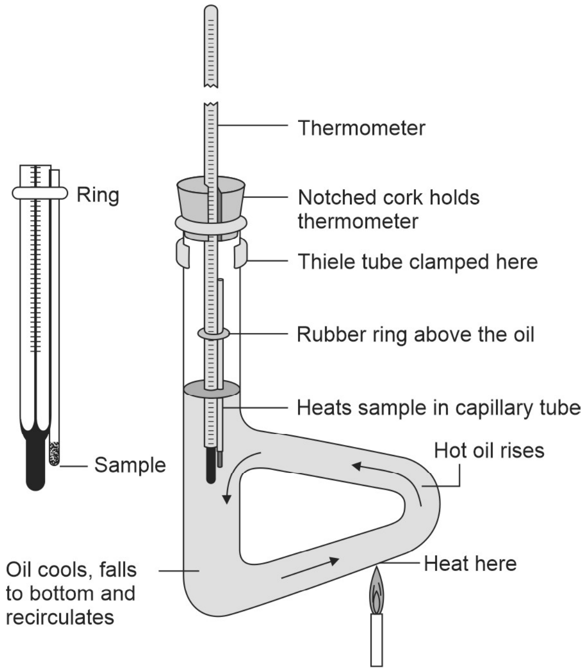


Fig. 1.4: Determine melting point

Boiling Point Determination and Distillation (Fig. 1.5)

The boiling point of a liquid is defined as the temperature at which the vapor pressure of the liquid equals the external pressure (usually 1 atmosphere). It is also defined as the

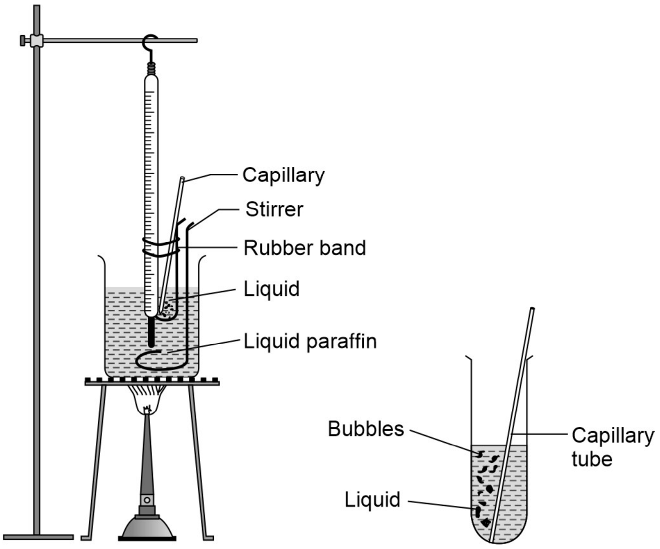


Fig. 1.5: Determine the boiling point

temperature at which vapor and liquid are in equilibrium at a given pressure. The boiling point, like the melting point, is a physical constant and may be used to identify unknown organic liquids. Distillation is the process of heating a liquid to its boiling point, condensing the vapor by cooling, and collecting the liquid distillate. It is a technique for the purification of liquids and for the separation of liquid mixtures. As the distillation progresses, the mixture will gradually have less of the more volatile component and its boiling point will gradually rise. Consequently, the distillate will contain a continually decreasing proportion of the more volatile component until finally all has been collected and the less volatile component is left as a residue.

In practice, separation of a liquid mixture into its components by a single distillation (simple distillation) is possible only when the boiling points of the components are 80 degrees or more apart. For mixtures of liquids having boiling points much less than 80 degrees apart, separation can be achieved only by fractional distillation. Such a distillation is equivalent to several repeated simple distillations. It uses a fractionating column which provides a large surface area for continuous heat exchange between the hot ascending vapor and the cooler descending liquid, thus resulting in a series of evaporations and condensations leading to separation of the two components. Vacuum distillation is a technique for the distillation of high boiling liquids, and for compounds that decompose at atmospheric pressure. At the low pressures employed, those compounds distil at much lower temperatures.

Applications of Crystallization

- Purification of seawater
- Separation of alum crystals from impure samples
- In the pharmaceutical industry, crystallization is used as a separation and purification process for the synthesis and isolation of co-crystals, pure active pharmaceutical ingredients (API), controlled release pulmonary drug delivery, and separation of chiral isomers.

PURIFICATION OF LIQUIDS

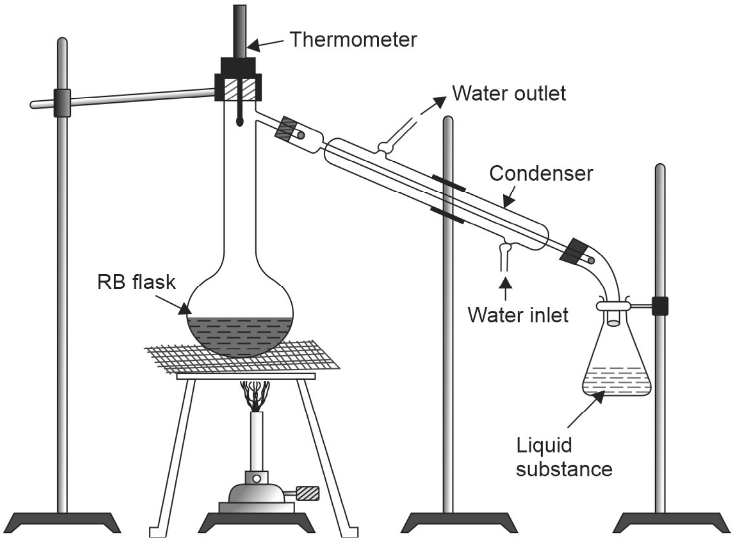
Distillation

The underlying principle behind distillation is that the mixture of liquids can be separated by the difference in their boiling points. The boiling point is defined as that temperature at which the vapour pressure of the liquid is equal to the atmospheric pressure. This method separates volatile liquids from non-volatile liquids. The setup is given in Fig. 1.6.

Distillation refers to the selective boiling and subsequent condensation of a component in a liquid mixture. It is a separation technique that can be used to either increase the concentration of a particular component in the mixture or to obtain (almost) pure components from the mixture. The process of distillation exploits the difference in the boiling points of the components in the liquid mixture by forcing one of them into a gaseous state.

It is important to note that distillation is not a chemical reaction but it can be considered as a physical separation process. An illustration describing the laboratory setup that is generally used to execute this process is provided below.

The distillation performed on a laboratory scale often uses batches of the liquid mixture whereas industrial distillation processes are generally continuous, requiring a constant composition of the mixture to be maintained.



The vapours of the substance formed are condensed and the liquid is collected in a conical flask.

Fig. 1.6: Distillation

Role of Raoult's law and Dalton's law: The temperature at which the vapor pressure of a liquid becomes equal to the pressure of the surrounding area is known as the **boiling point** of that liquid. At this temperature point, the liquid is converted into its vapor form via the formation of vapor bubbles at its bulk.

It is important to note that the boiling point of the liquid changes with the surrounding pressure. For example, the boiling point of water at sea level is 100ºC but its boiling point at an altitude of 1905 meters is 93.4ºC (since the atmospheric pressure is relatively lower at high altitudes).

For a mixture of liquids, the distillation process is dependent on Dalton's law and Raoult's law. As per **Raoult's law**, the partial pressure of a single liquid component in an ideal liquid mixture equals the product of the vapor pressure of the pure component and its mole fraction. According to **Dalton's law of partial pressures,** the total pressure exerted by a mixture of gases is equal to the sum of the partial pressures of all the constituent gases.

When a mixture of liquids is heated, the vapor pressure of the individual components increases, which in turn increases the total vapor pressure. Therefore, the mixture cannot have multiple boiling points at a given composition and pressure.

At the boiling point of a mixture of liquids, all the volatile constituent's boil. However, the quantity of a constituent in the resulting vapor is based on its contribution to the total vapor pressure of the mixture. This is why the compounds with higher partial pressures can be concentrated in the vapors whereas the compounds having low partial pressures can be concentrated in the liquid.

Since a component in the mixture cannot have zero partial pressure, it is impossible to obtain a completely pure sample of a component from a mixture via distillation. However, samples of high purity can be obtained when one of the components in the mixture has a partial pressure which is close to zero.

Types of Distillation

Some important types of distillation include:
- Simple distillation
- Fractional distillation
- Steam distillation
- Vacuum distillation (distillation under reduced pressure)
- Air-sensitive vacuum distillation
- Short path distillation
- Zone distillation

Simple Distillation

- This process is used to separate a liquid from solid or non-volatile impurities present in it.

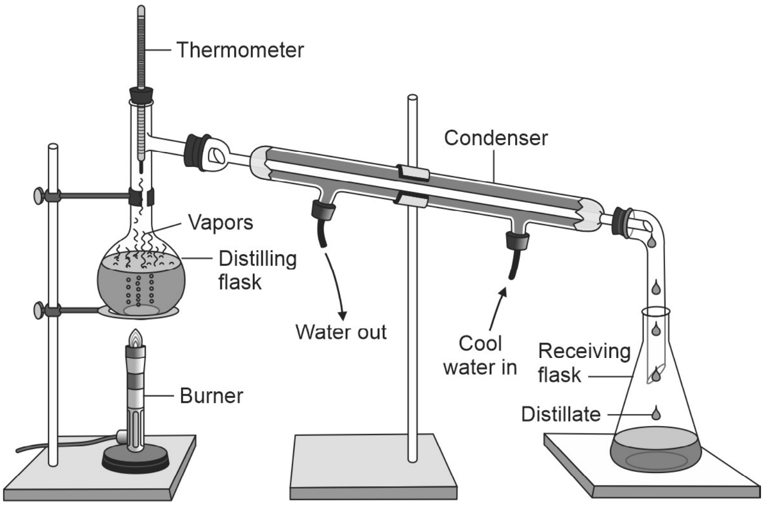


Fig. 1.7: Simple distillation

- Simple distillation involves heating the liquid mixture to the boiling point and immediately condensing the resulting vapors.
- This method is only effective for mixtures wherein the boiling points of the liquids are considerably different (a minimum difference of 25ºC).
- The purity of the distillate (the purified liquid) is governed by Raoult's law.

Fractional Distillation

Fractional distillation is the separation of a mixture into its component parts, or fractions, such as in separating chemical compounds by their boiling point by heating them to a temperature at which several fractions of the compound will evaporate. It is often used to separate mixtures of liquids that have similar boiling points. It involves several vaporization-condensation steps (which takes place in a fractioning column). This process is also known as rectification. The apparatus required to perform a fractional distillation on a mixture is listed below.

- Round-bottom flask or distilling flask.
- A source of heat, which can be a fire or a hot bath.
- Receiving flask to collect the condensed vapors.
- Fractioning column.
- Thermometer to measure the temperature in the distilling flask.
- Condenser.
- Standard glassware.

When heated, the liquid mixture is converted into vapors that rise into the fractioning column. The vapors now cool and condense on the walls of the condenser. The hot vapors emanating from the distilling flask now heat the condensed vapor, creating new vapors.

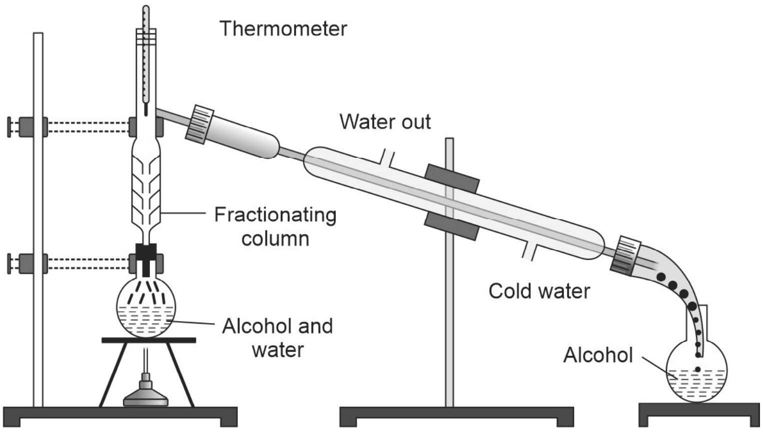


Fig. 1.8: Fractional distillation

Many such vaporization-condensation cycles take place and the purity of the distillate improves with every cycle. An illustration depicting a fractional distillation setup is provided below.

Steam Distillation

- Steam distillation is often used to separate heat-sensitive components in a mixture.
- This is done by passing steam through the mixture (which is slightly heated) to vaporize some of it. The process establishes a high heat-transfer rate without the need for high temperatures.

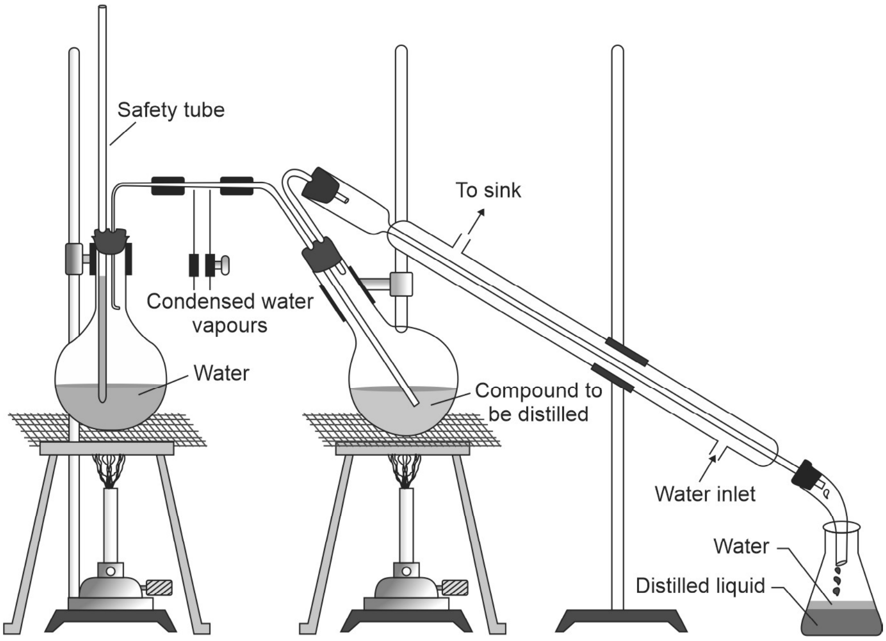
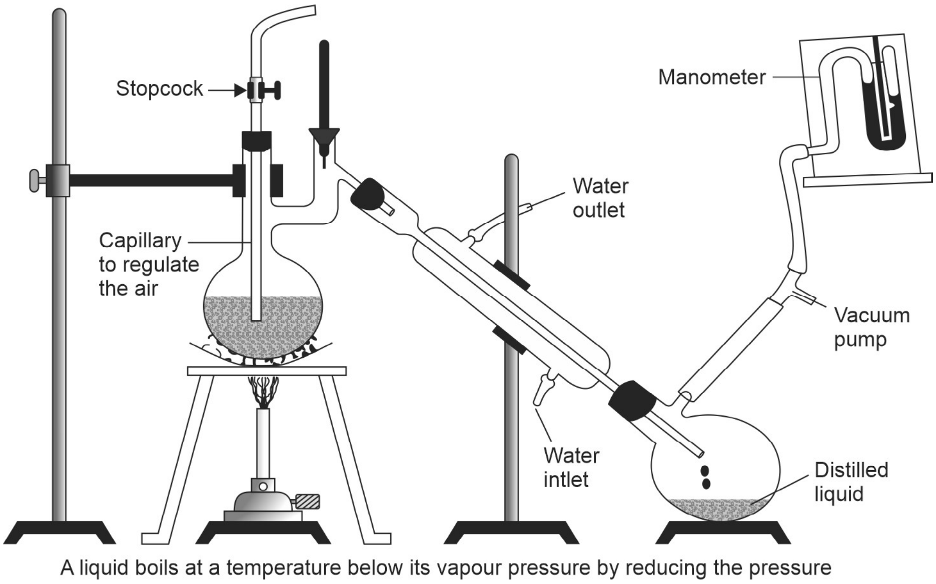


Fig. 1.9: Steam distillation

- The resulting vapor is condensed to afford the required distillate.
- The process of steam distillation is used to obtain essential oils and herbal distillates from several aromatic flowers/herbs.

Vacuum Distillation (Distillation under Reduced Pressure)

- **Vacuum distillation** is a method of distillation whereby the pressure above the liquid mixture to be distilled is reduced to less than its vapor pressure (usually less than atmospheric pressure).



A liquid boils at a temperature below its vapour pressure by reducing the pressure

Fig. 1.10: Vacuum distillation

- This distillation method works on the principle that boiling occurs when the vapor pressure of a liquid exceeds the ambient pressure. Vacuum distillation is used with or without heating the solution
- Vacuum distillation is ideal for separating mixtures of liquids with very high boiling points.
- In order to boil these compounds, heating to high temperatures is an inefficient method. Therefore, the pressure of the surroundings is lowered instead.
- The lowering of the pressure enables the component to boil at lower temperatures. Once the vapor pressure of the component is equal to the surrounding pressure, it is converted into a vapor.
- These vapors are then condensed and collected as the distillate. The vacuum distillation method is also used to obtain high-purity samples of compounds that decompose at high temperatures.

Air-Sensitive Vacuum Distillation

For compounds that are sensitive to air and readily react with it, the vacuum distillation process is carried out but the vacuum must be replaced with an inert gas once the process is complete. Such a process is often referred to as air-sensitive vacuum distillation.

Short Path Distillation

Short path distillation is used to purify a small quantity of a compound that is unstable at high temperatures. This is done under lowered pressure levels and generally involves the distillate traveling a very small distance before being collected (hence the name 'short path'). The reduced distance traveled by the distillate in this method also reduces the wastage along the walls of the apparatus.

Zone Distillation

The process of zone distillation involves the partial melting of a substance and the condensation of the resulting vapors to obtain a pure distillate. This is carried out in a long container with the help of a zone heater.

Important Applications

The method of distillation has a considerable history, dating back to 3000 BC. Evidence suggests that the distillation of alcohol was developed as far back as the 9th century. Some important applications of distillation are listed below.

- Distillation plays an important role in many water purification techniques. Many desalination plants incorporate this method in order to obtain drinking water from seawater.
- Distilled water has numerous applications, such as in lead-acid batteries and low-volume humidifiers.
- Many fermented products such as alcoholic beverages are purified with the help of this method.
- Many perfumes and food flavorings are obtained from herbs and plants via distillation.
- Oil stabilization is an important type of distillation that reduces the vapor pressure of the crude oil, enabling safe storage and transportation.
- Air can be separated into nitrogen, oxygen, and argon by employing the process of cryogenic distillation.

- Distillation is also employed on an industrial scale to purify the liquid products obtained from chemical synthesis.

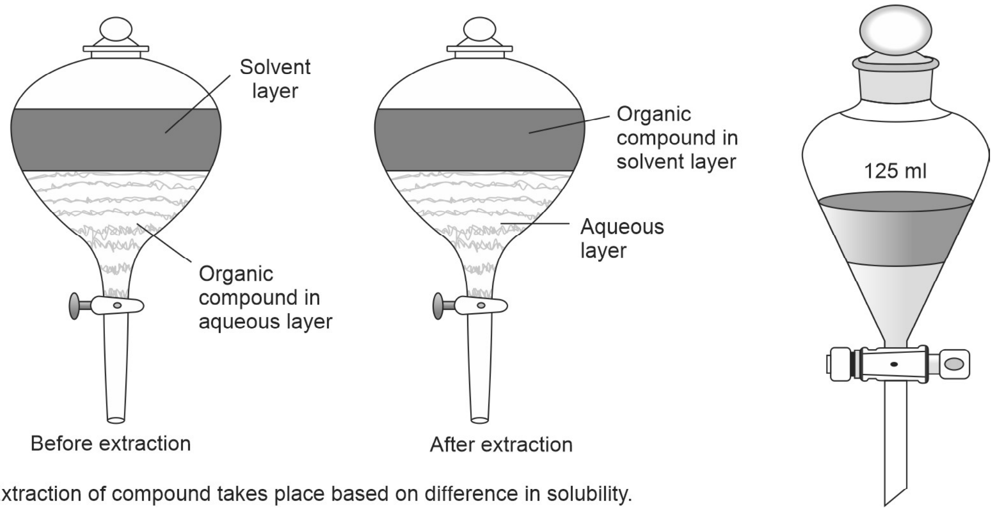
Extraction

Extraction techniques in used to separate and transfer specific compounds from a mixture into a different solvent or phase. If the substance is extracted from a solid phase, the process is called solid-liquid extraction, as in the isolation of caffeine from tea leaves by means of hot water. The most commonly used extraction technique is liquid-liquid extraction, which involves the use of a separatory funnel. A compound of interest is placed directly into the funnel that contains a mixture of two liquid layers that are typically a mixture of an aqueous solution and an organic solvent. Since the organic solvent is immiscible, the specific components of the original compound will move from either the aqueous or organic layer, depending on their hydrophilicity or hydrophobicity, respectively.

Differential Extraction

This method is used for immiscible liquids, that is, liquids that do not mix together. For example, oil and water are immiscible.

The immiscible liquids are taken in a separating funnel and left undisturbed. After a while, they separate out according to their specific gravities, with the heavier liquid at the bottom. Then they are later collected.



Extraction of compound takes place based on difference in solubility.

Fig. 1.11: Differential extraction

Substances can also be separated according to their preferential solubilities in the liquid. For example, if phenol is to be extracted, it can be preferentially extracted using NaOH solution as one of the liquids used.

Chromatography

Chromatography is an important separation technique used to separate, identify and purify the components present within a given mixture for analysis purposes. The basic principle behind any chromatography technique is that the molecules of a mixture are placed onto the surface of a solid material, which is referred as the stationary phase. The mobile phase of this technique is a liquid or gas is allowed to move slowly on the stationary phase. Due to which the components of the mixture start separating from one another.

Some of the most common chromatography methods that will be utilized in an organic chemistry lab include column, ion-exchange, affinity, paper, thin-layer, gas and high-performance liquid chromatography (HPLC). Two principles are basically involved in chromatography: adsorption (as in thin layer chromatography) and partition (as in paper chromatography), and certain terms are common to both types of chromatography. In adsorption chromatography, separation depends on the selective desorption of the components of a mixture by the eluent (mobile phase) from the surface of a solid adsorbent (stationary phase). The adsorbent may be packed in a column (column chromatography) or spread as a thin layer on a glass plate as in thin-layer chromatography. In partition chromatography, separation depends on partition of the components of a mixture between the stationary and mobile phases. The mobile phase may be a liquid (liquid-liquid partition chromatography) or a gas (gas-liquid partition chromatography).

Each of these laboratory techniques requires a variety of different supplies and equipment to be performed. For example, thin-layer chromatography (TLC) utilizes an absorbent material like alumina, silica gel or cellulose as its stationary phase that is placed within a glass container or plate for the separation procedure. Comparatively, HPLC requires an HPLC device that is equipped with a solvent depot, high-pressure pump, and commercially prepared column that is suitable for the researcher's specific project, detector, recorder and a computerized system that is used to record all obtained measurements.

Chromatography is of two types:

- Adsorption chromatography (column chromatography, thin layer chromatography).
- Partition chromatography.

Adsorption Chromatography

It is based on the principle that the constituents are adsorbed on an adsorbent in varying degrees. The adsorbents used are generally silica gel or alumina. When a mobile phase

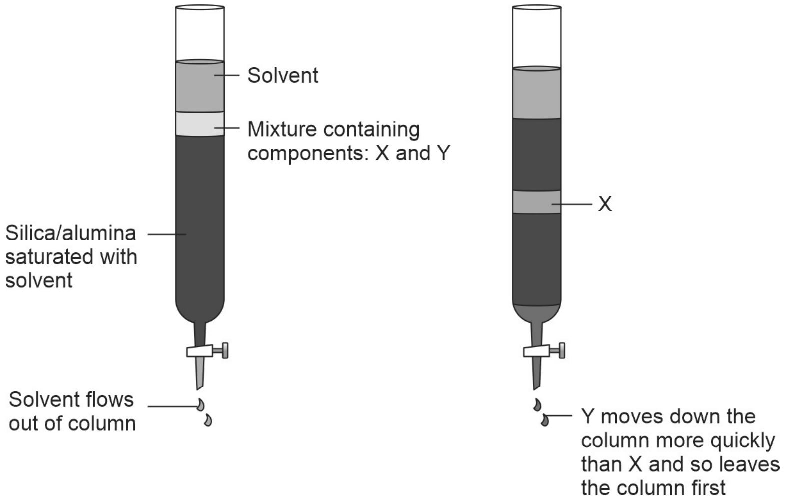


Fig. 1.12: Adsorption chromatography

moves over the fixed phase, different constituents of the mixture get adsorbed at various distances over the fixed phase.

Adsorption Chromatography Principle

Adsorption chromatography involves the analytical separation of a chemical mixture based on the interaction of the adsorbate with the adsorbent. The mixture of gas or liquid gets separated when it passes over the adsorbent bed that adsorbs different compounds at different rates.

Adsorbent

A substance which is generally porous in nature with a high surface area to adsorb substances on its surface by intermolecular forces is called adsorbent. Some commonly used adsorbents are silica gel H, silica gel G, silica gel N, silica gel S, hydrated gel silica, cellulose microcrystalline, alumina, modified silica gel, etc.

Adsorption Chromatography Procedure

Before starting with the adsorption chromatography experiment let us understand the two types of phases and the types of forces involved during the mixture separation process.

- **Stationary phase:** Adsorbent is the stationary phase in adsorption chromatography. The forces involved help to remove solutes from the adsorbent so that they can move with the mobile phase.
- **Mobile phase:** Either a liquid or a gas is used as a mobile phase in adsorption chromatography. Forces involved help to remove solutes from the adsorbent so that they can move with the mobile phase. When a liquid is used as a mobile phase it is called LSC (liquid-solid chromatography). When a gas is used as a mobile phase it is called GSC (gas-solid chromatography).

Apparatus

Chromatography jar: The glass jar has a lid. It helps to maintain a proper environment during separation.

Thin-layer chromatography plate: Borosilicate glass plate with size 20 × 20 cm, 20 × 5 cm, 20 × 10 cm.

Capillary tube: Sample mixture is applied to TLC with the help of this tube.

Mobile phase: Liquid or gas

Stationary phase: Adsorbents

Types of Adsorption Chromatography

1. **Thin layer chromatography:** It is a chromatography technique where the mobile phase moves over an adsorbent. The adsorbent is a thin layer which is applied to a solid support for the separation of components. The separation takes place through differential migration which occurs when the solvent moves along the powder spread on the glass plates. This technique of TLC is useful in determining the type and number of ingredients in the mixture.

   Mobile phase: This phase in TLC can either be a single liquid or mixture of liquids. Some commonly used liquids are ethanol, acetone, methanol, chloroform. Stationary phase—adsorbents.

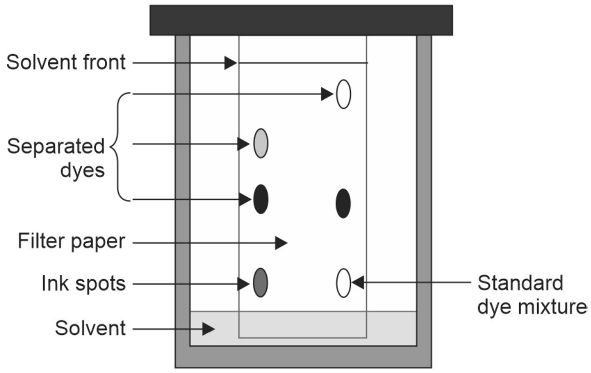


Fig. 1.13: Technique of thin layer chromatography

Paper Chromatography

The separation of a mixture is done by passing the solvent through a chromatographic paper which is called paper chromatography. In the stationary phase chromatography, the water is absorbed that is present in the cellulose whereas the mobile phase consists of organic solvent that is immiscible with the stationary phase. This type of chromatography mainly works on the principle of partition and absorption.

Paper is used as a stationary phase, the filter paper is selected depending on the four factors, which are the thickness of the paper, purity of the solvent, flow rate, and strength of the paper. The widely used type of filter paper is Whatman filter paper. The mobile phase in paper chromatography is selected depending on the R_f value, if the R_f value ranges from 0.2 to 0.8, then it is selected for the process.

There are different types of paper chromatography:

1. **Ascending paper chromatography:** In this technique, the solvent moves in an upward direction.
2. **Descending paper chromatography:** The flow of solvent happens due to the gravitational pull and the capillary action it is directed downwards.
3. **Ascending-descending paper chromatography:** After a particular point the movement of solvent occurs in a two-direction way. Initially, it travels in an upward direction on the paper that is folded around the rod. When the solvent crosses the paper it travels in a downward direction.
4. **Circular or radial paper chromatography:** The sample is present on the filter paper that is circular, it is allowed to dry and once the sample is dried it is tied horizontally on the solvent containing petri dish.
5. **Two-dimensional paper chromatography:** Substances that have the same R_f value can be separated by using this technique.

Column Chromatography

The technique in which the solutes of a solution are entitled to travel down through a column, where the individual components are adsorbed by the stationary phase. Based on the affinity towards adsorbent the components take positions on the column. The most strongly adsorbed component is seen at the top of the column. This technique is useful in determining the type and number of ingredients in the mixture and helpful for collecting the separated components.

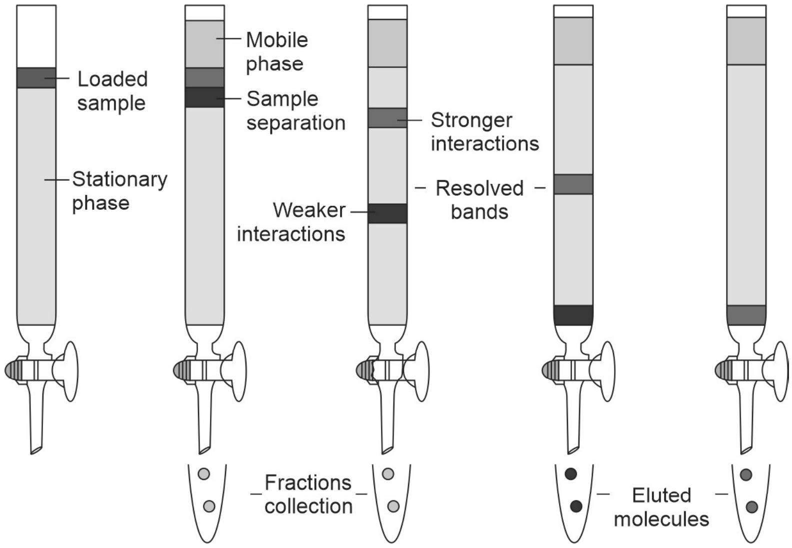


Fig. 1.14: Column chromatography

Gas-Solid Chromatography

The principle of separation in GSC is adsorption. It is used for solutes which have less solubility in the stationary phase. This type of chromatography technique has a very limited number of stationary phases available and, therefore, GSC is not used widely.

Adsorption Chromatography Experiment (Thin Layer Chromatography)

- Take a clean and dry chromatographic jar.
- To make sure that the environment in the jar is saturated with solvent vapours, a paper soaked in the mobile phase is applied to the walls.
- Add the mobile phase to the jar and close it.
- Maintain equilibrium
- Mark the baseline on the adsorbent.
- Apply sample to TLC plate with the help of a capillary tube and allow it to dry.
- Put the plates in the jar and close it.
- Wait until the solvent moves from the baseline.
- Take out the TLC plate and dry it.
- Spray suitable detecting agent, dry then calculate R_f value.

Adsorption Chromatography Applications

- Adsorption chromatography is used for separation of amino acids.
- It is used in the isolation of antibiotics.
- It is used in the identification of carbohydrates.
- It is used to separate and identify fats and fatty acids.
- It is used to isolate and determine the peptides and proteins.

Depending on the nature of stationary and mobile phase, following chromatographic techniques are used as shown in Table 1.1.

Table 1.1: Chromatography techniques

S. No.	*Type of Chromatography*	*Mobile/Stationary phase*	*Uses*
1.	Adsorption/column chromatography	Liquid/solid	Large scale separation
2.	Thin layer chromatography	Liquid/solid	Qualitative analysis (identification and characterization of organic compounds)
3.	High performance liquid chromatography	Liquid/solid	Qualitative and quantitative analysis
4.	Gas liquid chromatography	Gas/liquid	Qualitative and quantitative analysis
5.	Partition chromatography/ ascending paper chromatography	Liquid/liquid (organic solvent/ polar solvent)	Qualitative and quantitative analysis of polar organic compounds. It is used to separate coloured chemicals or compounds

DETERMINATION OF MELTING POINT AND BOILING POINT

The property of an organic compound which is most frequently determined as a criterion of purity is the *melting-point,* because in general it may be said that a pure compound has usually a sharp melting-point, whereas an impure substance has an indefinite melting-point, and will therefore melt slowly and indecisively over a range of several degrees. The actual possibilities which may be revealed by a melting-point determination may be summarized as follows.

Melting Point Sharp

Substance chemically pure. This is almost invariably the cause of a sharp melting-point. Substance is a eutectic mixture of two or more compounds. The chance of a given mixture containing two compounds in just the proportion to give a sharp-melting eutectic mixture is so remote that this possibility may be neglected.

Melting Point Indefinite

The substance is *impure.* This is almost invariably the cause of an indefinite melting-point. The substance is *pure*, but on warming undergoes slight thermal decomposition before the melting-point is reached, and the decomposition products then act as impurities and depress the melting-point.

The compound whose melting point is to be determined is powdered. A capillary tube is approximately 2″ length is sealed at one end by heating in a bunsen flame. It is then filled up to about one cm (1 cm) length with the powdered substance. The capillary is then attached to the lower end of the thermometer. The thermometer is now placed in a small beaker filled with paraffin oil or concentrated sulphuric acid such that the liquid covers at least the filled length of the capillary. The beaker is gently heated and rise in temperature is observed carefully. The temperature at which the solid has completely changed into liquid is also heated. This range of temperature is recorded as (mp) range of substance.

A few drops of the liquid whose boiling point is too determined are taken in an ignition tube. A capillary tube sealed at the upper end is put inside the ignition tube and the latter is attached to the lower part of the thermometer with the help of a rubber thread. The thermometer along with the ignition tube is placed inside a pyrex test tube in such a way that the liquid inside the ignition tube is covered by conc. H_2SO_4. The test tube is heated slowly and the rise of the bubbles inside the capillary tube is carefully observed. The temperature at which a regular and speedy stream of bubbles begins to escape is taken to be the boiling point of the liquid this is recorded.

Procedure

For Melting Point

- Powder the compound (100 mg) with the help of spatula on clean watch glass.
- Seal one end of capillary tube. Fill it with finely powder sample to form a compact column.

Melting point can be determined by two ways:

a. Using paraffin bath:
    - Filled capillary is tied with lower end of thermometer.
    - Thermometer is placed in the paraffin bath. Heat the paraffin bath and note down the temperature at which substance starts melting and collapse of crystal.
    - The temperature at which it completely melts and become liquid is the melting point.

b. Using melting point apparatus:
    - This electrical heating apparatus has a large hole in center for thermometer and three small holes for capillaries which can be observed through a suitable magnifying eyepiece.
    - So, put the thermometer and capillary into melting point apparatus, switch it on and observe the capillary through magnifying eyepiece. When the compound starts melting, it is observed through eyepiece.
    - Note down the reading of thermometer when the compound starts melting and when the compound completely melts.
    - The temperature between the compound starts melting and the compound completely melts is the temperature range of given compound**.**

For Boiling Point

- A small quantity of liquid is filled in fusion tube.
- The capillary tube with sealed end uppermost is introduced into liquid.
- The fusion tube is attached to thermometer and it is immersed in paraffin bath.
- Paraffin bath is gradually heated and observe the capillary inside the fusion tube.
- The point at which there will be rapid and continuous bubbling from the capillary tube is the boiling point of the liquid.

Drying of Organic Substances

Drying Solids

Drying means removal of a solvent from a solid by evaporation. The rate of evaporation and thus the rate of drying can be increased by one (or all) of the following:

- Heating the chemical.
- Using a drying agent in a closed container to absorb the solvent.
- Reducing the atmospheric pressure.

Most solids are dried first by pressing them gently between folds of filter papers. Only chemicals which are *thermally stable* should be dried by heating. Most organic

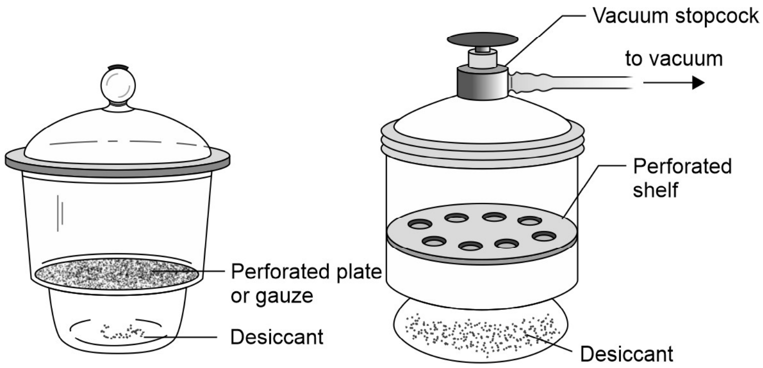


Fig. 1.15: Desiccator and vacuum desiccator

compounds with relatively high melting points, can be dried in an electric oven at 110°C to remove water, whereas organic compounds, many of which have relatively low melting points, need to be treated with more care and the oven temperature should be set between 30°C and 50°C below the melting point of the chemical. Substances which decomposes on heating are dried by keeping them in a vacuum desiccators containing a suitable dehydrating agents like fused calcium chloride, silica gel, concentrated sulphuric acid, solid sodium hydroxide or potassium hydroxide as desiccant (Fig. 1.15).

Drying Liquids

This usually means removing water from a liquid chemical or a solution of a chemical in a water-immiscible solvent. Organic liquids are generally dried by keeping them overnight in contact with dehydrating (desiccating) agents which does not react chemically with the liquid to be dried. Most commonly used dehydrating agents are quick lime, anhydrous calcium chloride, fused copper sulphate/calcium sulphate/magnesium sulphate/sodium sulphate, etc. We can dry liquids after evaporation or distillation. In both cases the liquid is placed in direct contact with the solid drying agent, i.e. the drying agent is added to the liquid or solution. Ideally the drying agent should be totally insoluble in the liquid, should not react with it, absorb the water quickly and efficiently, and be easily filtered off.

The purity of an organic compound can be ascertained by determining its some physical constants like melting point, boiling point, specific gravity, refractive index and viscosity. Generally sharp melting points in case of solids and boiling points in case of liquids are used as criteria for purity because a pure organic solid has a definite and sharp melting point while an impure substance has a lower and indefinite melting point.

EXPERIMENT 1: TO DETERMINE MELTING POINT OF GIVEN COMPOUND (BENZOIC ACID)

Requirements

Benzoic acid, capillaries, fusion tube, paraffin bath, melting point apparatus, and thermometer.

Theory

The change from solid to liquid state of a compound in heating is called melting and the temperature at which a solid in its pure form melts is called the melting point. Every pure solid has a characteristics melting point, therefore, determination of melting point helps in identification of the compound. Presence of impurities lowers the melting point of the solid. Thus, melting point also serves as a criterion of purity of a compound.

The physical properties of a compound, such as melting point and boiling point can provide useful information which can help in the identification of a sample or to establish its purity. These pages describe two common methods for determining melting point using:

1. A melt temp apparatus
2. A thiele tube set up.

The temperature at which a solid melt and becomes a liquid is the melting point. Since this requires that the intermolecular forces that hold the solid together must be overcome, the temperature at which melting occurs will depend on the structure of the molecule involved—an example of the relationship between structure and properties. Hence, different compounds tend to have different melting points.

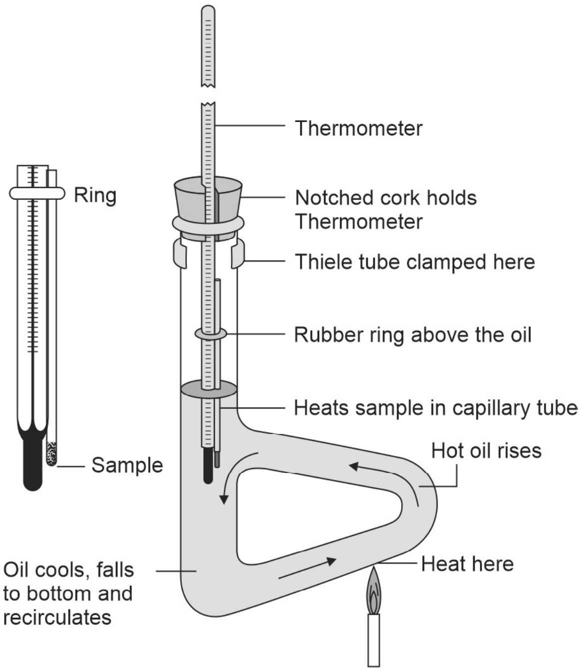


Fig. 1.16: Determine melting point

Procedure

1. Take benzoic acid on a tile and crush it into a fine powder.
2. Take a capillary tube and by heating one end close the end of the tube.
3. Hold the closed end of the capillary tube between your finger and thumb as shown in Fig. 1.16.
4. Dip the open end of the capillary tube in the finely powdered benzoic acid.
5. Fill the compound in the capillary tube to about a length of 1–2 cm by gently tapping the capillary.
6. Attach the thermometer to a capillary tube using a thread as shown in Fig. 1.16.

7. Clamp thiele tube on a burette stand and fill the tube with clear mineral oil at least 1 cm higher than triangular arm.
8. Attach thermometer, capillary and cork into the thiele tube adjusting the height so that sample is midway inside the tube.
9. Heat the apparatus gently on the side arm as thiele tube with bunsen burner.
10. Keep continuous watch of the temperature and note the temperature as soon as the substance starts to melt.
11. Note the temperature (t_1) as the substance begins to melt.
12. Make a note of the temperature (t_2) & (t_3) when the substance has completely melted.
13. The average temperature of the substance is determined.

Observation Table

Temperature observation of benzoic acid

Temperature observation of benzoic acid

S. no.	*Temperature*	*Observation*
1.	t_1	122°C
2.	t_2	122°C
3.	t_3	123°C

The melting point of benzoic acid ($t_1 + t_2 + t_3/3$) = 122 + 122 + 123/3 = 122°C

Precautions to be Taken during the Experiment

1. Make sure the sample of benzoic acid is dry and powdered.
2. Keep the capillary tube and the thermometer at a similar level.
3. Tightly pack the powder into the capillary tube without any air gaps.

Result

The melting point of organic compounds like benzoic acid is determined.

EXPERIMENT 2: TO DETERMINE THE BOILING POINT OF THE GIVEN ORGANIC COMPOUND (BENZENE)

Requirements

Benzene, liquid paraffin, beaker, thermometer and ignition tube.

Theory

The boiling point of a compound is the temperature at which it changes from liquid to a gas. The boiling point of a liquid is the temperature at which its vapour pressure becomes equal to atmospheric pressure.

It is the property often used to check the purity of the given compound. The physical properties of a compound, such as melting point and boiling point can provide useful information which can help in the identification of a sample or to establish its purity. Since the boiling point of an unknown sample under the same conditions (e.g. same pressure) is a constant, a measured boiling point can be compared to known values (e.g. literature value or the measured value of a known sample).

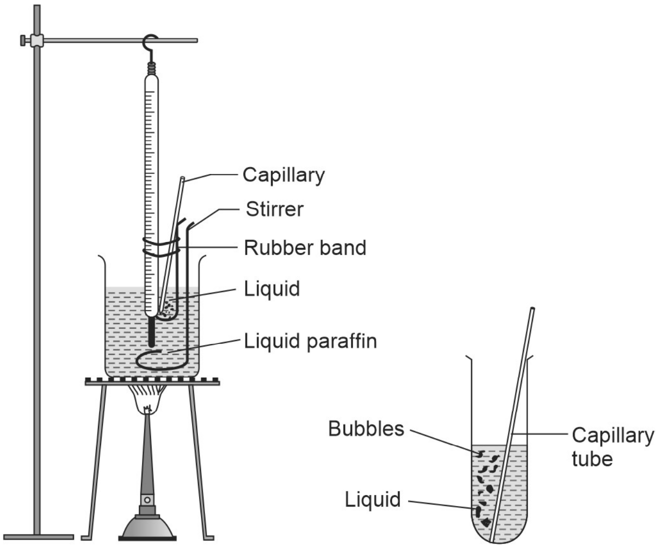


Fig. 1.17: Determine the boiling point

Since this used to be a very important method, there are tables and collections of boiling point data available and the boiling point at sea level (as a standard) is one of the physical properties of a compound that is commonly recorded and reported.

Procedure

1. Take a small amount of liquid in an ignition tube and place a capillary tube sealed at one of its end in an inverted position in the same ignition tube.
2. Attach the ignition tube with the thermometer by means of a rubber band in such a way that the lowers end of the ignition tube always remains in contact with the bulb of the thermometer.
3. Introduce whole of the arrangement into the beaker or boiling tube containing liquid paraffin in such a way that bulb of the thermometer dips in the liquid.
4. Heat the beaker gently with constant stirring until a stream of bubble gas goes outside the capillary tube rapidly. Note down the temperature.

Observation

Boiling point:

1. ...... °C
2. ...... °C
3. ...... °C

Mean boiling point = $(t_1 + t_2 + t_3)/3$ °C

Precaution

1. Capillary tube must be sealed at one end.
2. Capillary must be placed in an inverted position.
3. Heating should be slow and uniform.

Result

The boiling point of given solid substance is determined.

Chapter
2
Synthesis of Organic and Medicinal Compounds

EXPERIMENT 1: TO PREPARE AND SUBMIT 1,3-PYRAZOLE

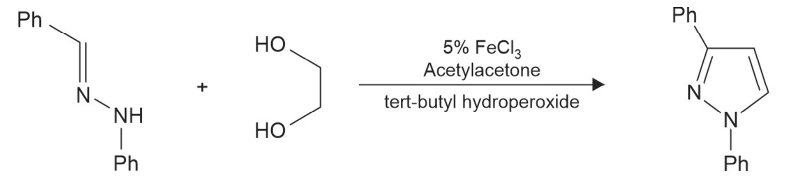
Requirements

1-benzylidene-2-phenylhydrazine, ethane-1,2-diol, ferric chloride, tert-butyl hydroperoxide, acetyl acetone, sodium chloride, ethyl acetate, sodium sulphate.

Theory

1,3-substituted pyrazole is prepared by cyclization of diarylhydrazone and vicinal diol in presence of ferric chloride and tert-butyl hydroperoxide (TBHP) which is also called regioselective synthesis of substituted pyrazole.

Chemical Reaction



1-Benzylidene-2-phenylhydrazine
Ethane-1,2-diol (vicinal diol)
1,3-Substituted pyrazole (1,3-Diphenyl pyrazol)

Procedure

1. About 4.55 g of 1-benzyledene-2-phenyl hydrazine is dissolved in the solution of 25 ml of ethane-1,2-diol (vicinal diol) and ferric chloride (5 mol %).
2. Then another solution of tert-butyl hydroperoxide (5.3 g) in 25 ml of acetyl acetone is added in to it.
3. The mix solution is kept maintaining at a temperature range of 90–100°C.
4. The mix solution is left to reach room temperature and stirred for 6 hours.
5. Then the content is poured into water and extracted with ethyl acetate three times.
6. The combined organic solution is washed with water, then with a saturated solution of sodium chloride, passed through sodium sulfate and evaporated under vacuum.
7. About 3.15 g of the final product is found.

Calculation

$$\text{Practical yield} = \text{......}\ \text{g}$$

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

$$\%\ \text{yield} = \text{......}\ \%$$

Result

1,3-pyrazole is prepared and submitted.

EXPERIMENT 2: TO PREPARE AND SUBMIT BENZIMIDAZOLE

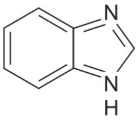
Requirements

o-Phenylenediamine, formic acid and NaOH.

Theory

Chemical formula: $C_7H_6N_2$
Molecular weight: 118
Melting point: 158–166°C

Structure



Benzimidazole

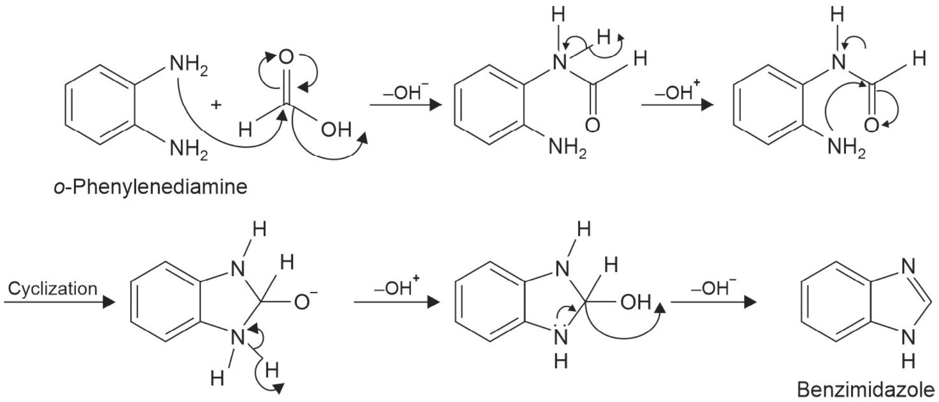
The principle involved in the synthesis of benzimidazole is Phillips reaction involves the condensation of ortho phenylenediamines with organic acids in presence of dilute mineral acids to furnish benzimidazoles. It is used as antifungal agent.

Mechanism

The two carbon nitrogen bonds in benzimidazole when disconnected give o-phenylenediamine and formic acid together. Initially one of the amino group is acylated with the organic acid in presence of mineral acid to furnish an N-acylated compound. In the next step, the other nitrogen is also acylated by making bond with the carbonyl carbon of the first acyl group leading to ring closure.

Chemical Reaction

Mechanism



Procedure

1. Place 27 g of *o*-phenylenediamine in a round bottom flask of 250 ml and add 17.5 g of 90% formic acid.
2. Heat the mixture on a water bath at 100°C for 2 hr.
3. Cool and add 10% sodium hydroxide solution slowly, with constant rotation on the flask, until the mixture is just alkaline to litmus.
4. Filter off the synthesized crude benzimidazole by using the pump, wash with ice water, drain well and wash again with 25 ml of cold water.

Recrystallization

1. Dissolve the synthesized product in 400 ml of boiling water, add 2 g of decolourising carbon and digest for 15 min.
2. Filter rapidly through a preheated Büchner funnel and a flask at the pump.
3. Cool the filtrate to about 10°C, filter off the benzimidazole, wash with 25 ml of cold water and dry at 100°C.

Calculation

Molecular weight of *o*-phenylenediamine ($C_6H_8N_2$) = 108 g/mol
Molecular weight of benzimidazole ($C_7H_6N_2$) = 118 g/mol

Theoretical Yield

108 g of *o*-phenylenediamine forms 118 g of benzimidazole.

Therefore, 27 g of *o*-phenylenediamine will form (X) g of benzimidazole.

$$X = (118 \times 27)/108 = 29.5 \text{ g}$$

Theoretical yield = 29.5 g
Practical yield = ... Y g

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

$$\% \text{ yield} = \frac{Y}{29.5} \times 100$$

Result

Benzimidazole is prepared and submitted.

EXPERIMENT 3: TO PREPARE AND SUBMIT BENZOTRIAZOLE

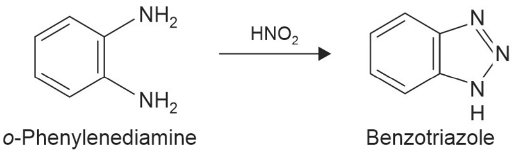
Requirements

o-Phenylenediamine, glacial acetic acid and sodium nitrite.

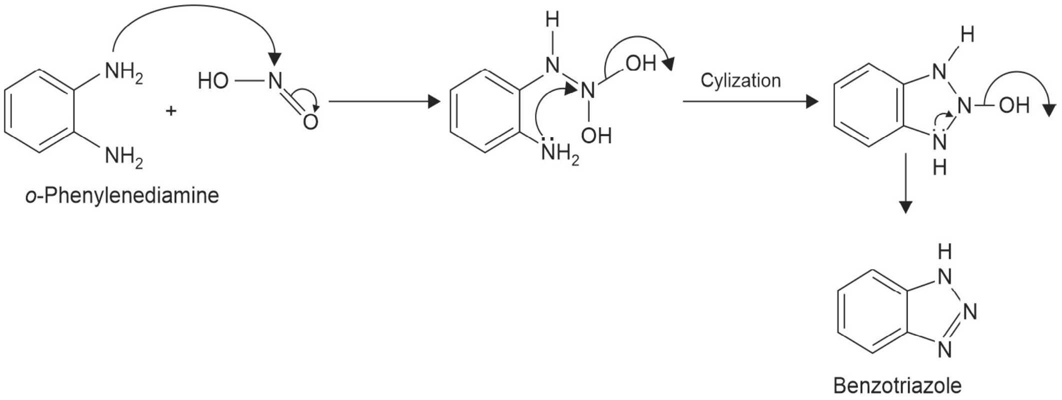
Theory

Benzotriazole can be prepared by treating *o*-phenylenediamine with nitrous acid to form mono-diazonium salt that follows spontaneous intramolecular cyclisation reaction to produce benzotriazole.

Chemical Reaction



Mechanism



Procedure

1. Dissolve 10.8 g of *o*-phenylenediamine in a mixture of 12 g of glacial acetic acid and 30 ml of water contained in a 250 ml beaker slight warming may be necessary.
2. Cool the clear solution to 15°C stir magnetically and then add a solution of 7.5 g of sodium nitrate in 15 ml of water in one portion.
3. The mixture gets warm and reaches a temperature of about 85°C within 2–3 min and then became cool while the colour of the mixture changes from deep red to pale brown.
4. Continue stirring for 15 min, by which time the temperature will have dropped to 35–40°C, and then thoroughly chill in an ice-water bath for 30 min.
5. Collect the product by vacuum filtration of the pale brown solid which separate and wash with three 30 ml portions of ice-cold water.

Recrystallization

1. Dissolve the solid in about 130 ml of boiling water, add decolourising charcoal, filter and allow the filtrate to cool to about 50°C before adding a few crystals of the synthesized product which have been retained for seeding.
2. Allow the mixture of attain room temperature slowly and then thoroughly chill in ice and collect the benzotriazole which separate as pale straw coloured needles.
3. A second crop may be obtained by concentrating the filtrate.

Calculation

Practical yield = ... g

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

% yield = ... %

Result

Benzotriazole is prepared and submitted.

EXPERIMENT 4: TO PREPARE AND SUBMIT 2,3-DIPHENYL QUINOXALINE

Requirements

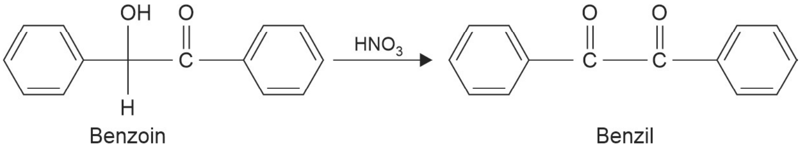
Benzoine, nitric acid, *o*-phenylenediamine, benzil and rectified spirit.

Theory

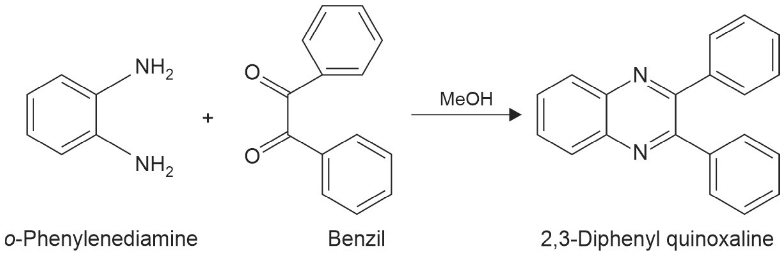
This is a method of condensation of an aryl 1,2-diamine with a 1,2-dicarbonyl compound by heating in a solvent like rectified sprit. Here condensation reaction of 1,2-diamines with α-diketones occurs with cyclization.

Chemical Reactions

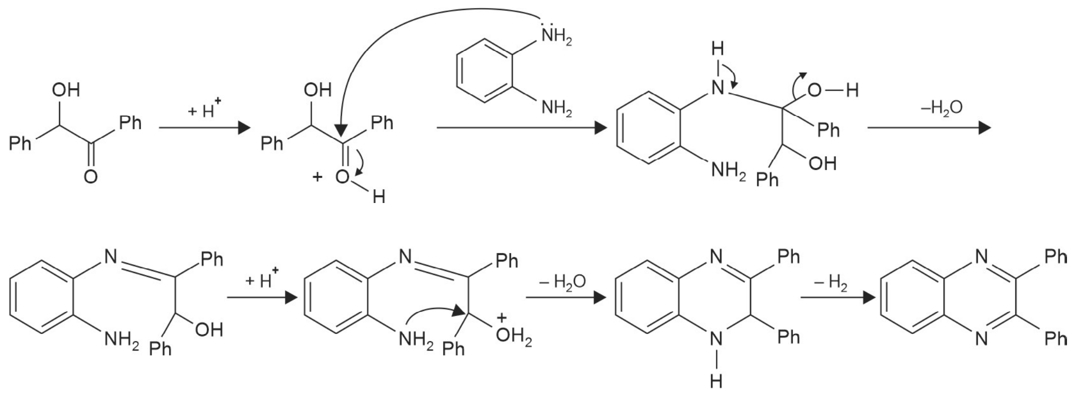
Step 1: Preparation of benzil from benzoin.



Step 2: Preparation of 2,3-diphenyl quinoxaline from benzil.



Mechanism



Procedure

Step 1: Preparation of benzil from benzoin.

1. Take a mixture of 20 g benzoin, and 100 ml conc. HNO_3 in a round bottom flask.
2. Heat on boiling water bath for 1.5 hr with occasional shaking until the evoluation of nitrogen ceases.
3. Then pour content into 300–400 ml ice cold water with shaking.
4. Filter out the product with suction, wash with cold water.
5. Recrystallized from ethanol.

Step 2: Preparation of 2,3-diphenyl quinoxaline from benzil.

1. Mix solutions of 2.1 g of benzil in 8 ml of methanol, and a solution of 1.6 of o-phenylenediamine in 8 ml methanol in a round bottom flask.
2. Heat on a water bath for 30 min, add water until a slight cloudiness persist and allow to cool.
3. Filter the separated crystals.
4. Recrystallize from aqueous ethanol to get brown needles of 2, 3-diphenyl quinoxaline having M.P. 125–126°C.

Calculation

$$\text{Practical yield} = \ldots\ldots \text{ g}$$

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

$$\%\text{ yield} = \ldots\ldots \%$$

Result

2,3-Diphenylquinoxaline is prepared and submitted.

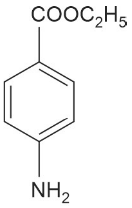
EXPERIMENT 5: TO PREPARE AND SUBMIT BENZOCAINE

Requirements

p-aminobenzoic acid (PABA), ethanol, concentrated H_2SO_4 and 10% sodium carbonate solution.

Theory

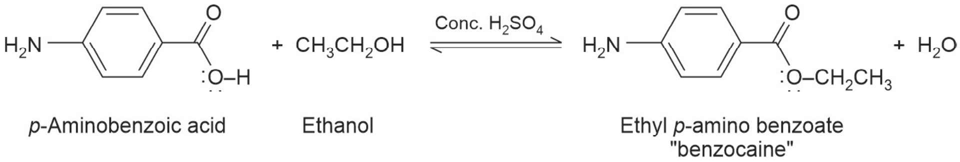
Chemical formula: $C_9H_{11}NO_2$
Molecular weight: 165
Melting point: 88–90°C
Chemical name: Ethyl *p*-aminobenzoate



Benzocaine

Benzocaine is the trade name for the local anesthetic known chemically as ethyl *p*-aminobenzoate, which is found in many creams and ointments used in the treatment of pain due to sunburn, minor burns, cuts, scrapes and insect bites. Benzocaine is structurally analogous to cocaine, lidocaine, and novocaine and is prepared by the esterification of *p*-aminobenzoic acid with ethanol. Aromatic esters are prepared by esterification of aromatic acids with alcohol in the presence of an Conc. H_2SO_4 or dry HCl which fastens the reaction. Benzocaine is an ester which can be prepared by esterification of PABA with ethanol in presence of HCl.

Chemical Reaction



Procedure

1. Place 3.6 g of *p*-aminobenzoic acid and 36 ml of ethanol in a 250 ml round bottom flask. Add a magnetic spin vane and stir the mixture to dissolve the solid acid.
2. With stirring, add 3 ml of concentrated sulfuric acid dropwise.
3. Addition of sulfuric acid causes precipitation of the hydrogen sulfate salt of *p*-aminobenzoic acid, however this precipitate will dissolve during the following reflux period as the hydrogen sulfate salt of the acid is converted into the hydrogen sulfate salt of the ester.
4. To prepare for reflux, attach a water-cooled condenser and heat the mixture so that it boils gently for 60–75 minutes.
5. When the reaction is complete, remove the reaction apparatus from the heat and allow it to cool. Transfer the solution to a conical flask containing about 30 ml of water.
6. The reaction mixture should dissolve completely in the water, since the ethyl *p*-amino benzoate is in the form of the hydrogen salt.
7. After the solution has cooled to room temperature, add the 10% sodium carbonate solution dropwise to neutralize the cooled reaction mixture.

8. As the pH of the solution rises, carbon dioxide will be produced and evolve as gas bubbles out of the solution.
9. Continue to add the sodium carbonate until the gas evolution ceases and the pH is above 8.
10. At this point the sulfuric acid is completely neutralized, and the ethyl *p*-amino benzoate precipitates.
11. Collect the precipitated of crude ethyl *p*-amino benzoate by vacuum filtration.
12. Wash the crystals with water on the funnel.
13. Recrystallized from a mixture of ethanol and water.

Calculation

Practical yield = ... g

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

% yield = ... %

Result

Benzocaine is prepared and submitted.

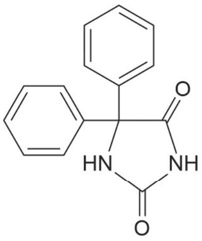
EXPERIMENT 6: TO PREPARE AND SUBMIT 5,5-DIPHENYLHYDANTOIN (PHENYTOIN) FROM BENZIL

Requirements

Benzoin benzil, urea, sodium hydroxide, ethanol, nitric acid and hydrochloric acid.

Theory

Chemical formula: $C_{15}H_{12}N_2O_2$
Molecular weight: 252
Melting point: 295–298°C
Chemical name: 5,5-diphenylhydantoin

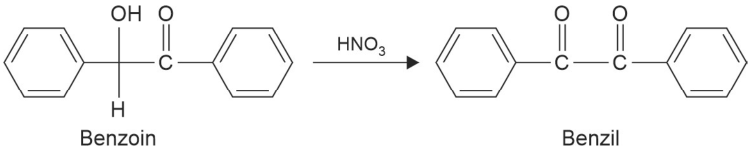


Phenytoin

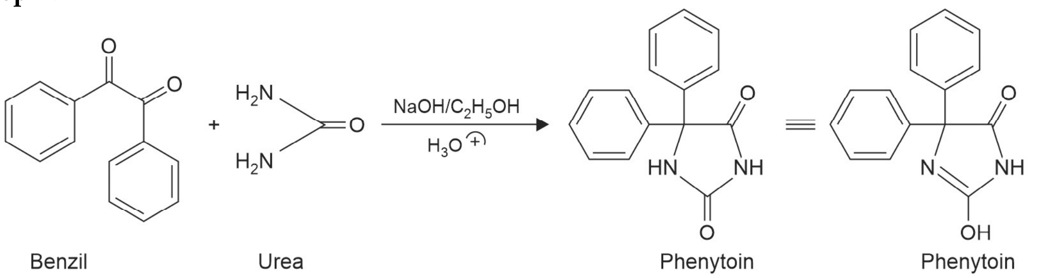
The principle involved in this reaction is pinacol–pinacolone rearrangement which is a is a method for converting a 1,2-diol to a carbonyl compound called pinacol which later undergoes a rearrangement and dehydration to form a monoketone called pinocolone. In this reaction aromatic diketone benzil reacts with urea to form an pinacol. Later this undergoes rearrangement to form pinacolone nothing but 5,5-diphenyl-hydantoin (phenytoin). Base catalyzed reaction between benzyl and urea is used for synthesis of phenytoin. The reaction is proceeding via intramolecular cyclisation to from an intermediate heterocyclic pinacol, which on acidification yield hydantoin as a result of 1, 2-diphenyl shift in pinacol rearrangement reaction.

Chemical Reactions

Step 1:



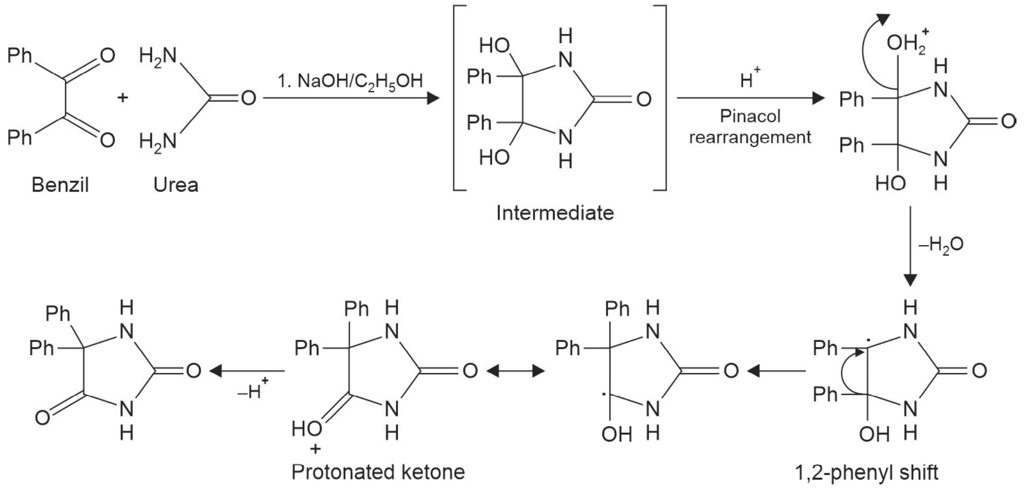
Step 2:



Mechanism

This reaction mechanism involves the three steps.

1. Protonation of 1,2-diol
2. Generation of carbonium ion by loss of water molecule
3. 1,2- shift of alkyl group to form a ketone



Procedure

Step 1: Preparation of benzil from benzoin.

1. Take a mixture of 20 g benzoin, and 100 ml conc. HNO_3 in a round bottom flask.
2. Heat on boiling water bath for 1.5 hr with occasional shaking until the evoluation of nitrogen ceases.

3. Then pour content into 300–400 ml ice cold water with shaking.
4. Filter out the product with suction, wash with cold water.
5. Recrystallized from ethanol.

Step 2: Preparation of phenytoin from benzil.

1. Place 5.3 g of benzil, 3.0 g of urea, 15 ml of aqueous sodium hydroxide solution (30%) and 75 ml of ethanol in a 100 ml round bottomed flask.
2. Set up a reflux condenser with the flask and boil using an electric heating mantle for at least 2 hr.
3. Cool to room temperature, pour the reaction mixture into 125 ml of water and mix carefully.
4. Allow the reaction mixture to stand for 15 min and then filter the product under suction to remove an insoluble by product.
5. Render the filtrate strongly acidic with concentration hydrochloric acid, cool in ice water and immediately filter off the precipitated product under suction.
6. Recrystallise at least once from ethanol to obtain pure phenytoin.

Calculation

Practical yield = ... g

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

% yield = ... %

Result

5,5-Diphenylhydantoin (phenytoin) is prepared and submitted.

EXPERIMENT 7: TO PREPARE AND SUBMIT PHENOTHIAZINE

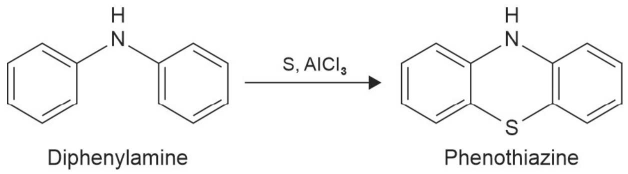
Requirements

Diphenylamine, sulfur, anhydrous aluminum chloride, water and dilute alcohol.

Theory

Phenothiazine is a class of agents exhibiting antiemetic, antipsychotic, antihistaminic, and anticholinergic activities. Phenothiazines antagonize the dopamine D_2-receptor in the chemoreceptor trigger zone (CTZ) of the brain, potentially preventing chemotherapy-induced emesis.

Chemical Reaction



Procedure

1. 22 g of diphenylamine, 8.2 g of sulfur, and 3.2 g of anhydrous aluminum chloride are melted together.
2. The reaction sets 140–150° C with the rapid evolution of hydrogen sulfide; by lowering the temperature, a few degrees the reaction can be slackened.
3. When the reaction has moderated, the temperature is raised to 160° C for a time.
4. The melt, when cool, is ground up and extracted, first with water and then with dilute alcohol.
5. The residue consists of almost pure phenothiazine.
6. It can be recrystallised from alcohol.

Calculation

$$\text{Practical yield} = \text{......}\ \text{g}$$

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

$$\%\ \text{yield} = \text{......}\ \%$$

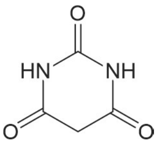
Result

Phenytoin is prepared and submitted.

EXPERIMENT 8: TO PREPARE AND SUBMIT BARBITURIC ACID

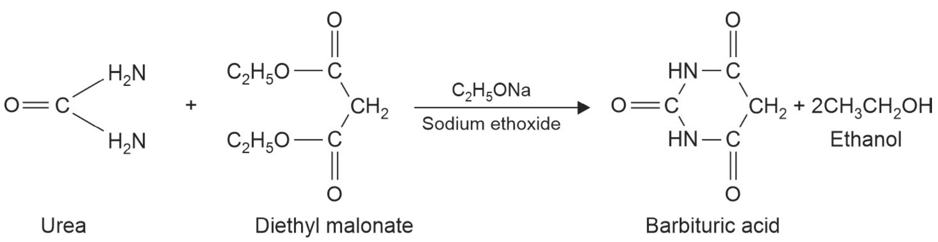
Theory

Chemical formula: $C_4H_4N_2O_3$
Molecular weight: 128
Melting point: 245 °C
Chemical name: 2,4,6-pyrimidinetrione



Barbituric acid (malonyl urea or 6-hydroxyuracil) is an organic compound based on a pyrimidine heterocyclic skeleton. It is an odorless powder soluble in water. Barbituric acid is the parent compound of barbiturate drugs, although barbituric acid itself is not pharmacologically active. Barbituric acid is used for synthesis of various hypnotic and sedative agents. These derivatives have profound effect on central nervous system.

Chemical Reaction



Procedure

1. Place 11.5 g sodium and add 250 ml absolute ethanol in a round bottom flask.
2. When all sodium has reacted add 80 g of diethyl malonate followed by 30 g urea solution in 250 ml of hot absolute ethanol.
3. Shake well the mixture, fit a calcium guard tube to the top of condenser and refluxes the mixture for 1 hr in the oil bath heated to 110°C.
4. A white solid separated treat it with 450 ml hot water and then with conc. HCl continuous stirring until the solution is acidic.
5. Filter the resulting clear solution and keep it in a refrigerator.

Result

Barbituric acid is prepared and submitted.

EXPERIMENT 9: DETERMINATION OF PARTITION COEFFICIENT OF SALICYLIC ACID

Requirements

Sodium salicylate solution, water and ferric nitrate.

Theory

Chemistry is a material science, dealing with the study of physical and chemical properties of the matter found in the universe. There are many disciplines in chemistry dealing with different materials and properties, like inorganic chemistry, organic chemistry, physical chemistry, pharmaceutical chemistry, analytical chemistry, etc. The analytical chemistry is a special branch of chemistry dealing with the determination of chemicals, quantity wise and quality wise.

The analytical chemistry uses the knowledge available in other branches of chemistry, like inorganic chemistry, organic chemistry, physical chemistry, and many principles of physics. The uses and applications of analytical chemistry are wide, and practically, in every aspect of human life, analytical chemistry is involved in some way or other, say, in clinical chemistry, pharmaceutical chemistry, forensic chemistry, in commerce, in customs department and so on. The measurement of partition coefficient is a typical analytical procedure using many theoretical principles of various branches of chemistry.

It denotes the differential amounts of the substances found at equilibrium conditions in the organic phase and the aqueous phase for a set of conditions like concentration, pH, temperature, etc. This lab study aims at and involves, in addition to learning partitioning technique, electrochemical applications: the pH measurement, colorimetric measurement, computational techniques, and calculation procedures.

The partition coefficient study assumes significance, because it finds use in pharmaceutical chemistry for drug design, development, and delivery, pesticide design, soil chemistry, designing of chemical plants by chemical engineers, and also for chemists and scientists working on liquid–liquid equilibrium data.

Procedure

Sample Preparation

Sodium salicylate solution of 0.2 g mol per liter (mol) was taken for this study. From this stock standard solution four test samples, named A to D, were prepared. 10 ml of

0.2 mol standard solution was pipette into each of the four 100 ml volumetric flasks marked A to D and diluted to the mark with four buffer solutions of different pH and mixed thoroughly. So the concentration of the resultant diluted samples was 0.02 mol each.

Partitioning

Aliquots of 25 ml of the above diluted samples, 4 no. were taken in 4 separating funnels. Then, 25 ml of the given oil was added in each of the 4 separating funnels, marked A to D, and mixed thoroughly and gently by inverting and rotating for 10 minutes. Then the mixture in the separating funnels was allowed to settle thoroughly. After the aqueous and organic layers became clear, the aqueous layers of the four separating funnels were drained into four glass beakers marked A to D.

pH Measurement of Aqueous Phase

The pH of the four partitioned aqueous samples were measured using a pH meter.

Determination of Salicylate Concentration in the Aqueous Phase

For determining the salicylate concentration, colorimetric method was adopted where the absorbance of the iron-salicylate complex was measured. The procedure adopted for developing the standard and test samples is given below.

Preparation of Standard Colour Solutions

Four different standard solutions of sodium salicylate, namely 0.00125 mol, 0.0025 mol, 0.00375 mol and 0.005 mol were prepared along with a blank.

Five test tubes were taken. The first one was marked as 1 (blank), and the others as 2, 3, 4, and 5.

To the blank, 1 ml of water was added, and in the others, one ml each of the prepared standards was added. Then 2 ml of the given ferric nitrate was added to all the test tubes. Then 5 ml of water was added into all the five test tubes. All the test tubes were shaken gently to mix the contents thoroughly and waited for some time for the complete development of the color. The five solutions represented 0.0000 mol, 0.00125 mol, 0.0025 mol, and 0.00375 mol and 0.005 mol salicylic acid concentration respectively.

Preparation of Calibration Graph

The colorimeter (spectrophotometer) was set at the wave length of 624 nm. Placed the blank in the cuvete in the colorimeter and adjusted the absorbance as zero. Then the other standard solutions were placed one by one and noted the absorbance readings. Calibration graph was plotted, plotting concentration of salicylic acid in x axis and absorbance at the y axis.

Preparation of Test Samples

10 ml of each of the four partitioned aqueous layers were diluted with water to 50 ml, thus making a diluted sample. From these, 1 ml solution each were placed in four test tubes, marked A, B, C, and D. Then, 2 ml ferric nitrate and 5 ml water were added in all the four test tubes and treated similar to the standard tubes.

Measurement of Salicylic Acid Concentration of the Test Samples

The absorbance of all the four test samples were measured similar to the standards. The Salicylic acid concentration of the test samples were arrived from the calibration graph.

The concentration arrived was of the diluted samples. So, the concentration of the partitioned aqueous phase was multiplied 5 times to get the concentration of the salicylic acid. This gives the Cw, i.e. the concentration of the salicylic acid in the partitioned aqueous solution.

Determination of CO

The Cw was subtracted from the concentration of the buffered solution, i.e., 0.02 mol, to get the CO.

Determination of Hydrogen Ion Concentration

From the pH of the four partitioned aqueous solutions, hydrogen ion concentrations were calculated.

Calculation

Calculation of the concentration of salicylate added to each separating funnel:

The salicylic acid concentration of the sample taken = 0.2 g. mol/Liter. 10 ml of this solution was diluted with buffer to 100 ml. So, the concentration of the diluted solutions, added to each separating funnel, taken for the:

Partition experiment were 0.2 × 10/100 = 0.02 g mol/L each.

Result

Partition coefficient of salicylic acid is determination.

EXPERIMENT 10: TO DETERMINE PERCENTAGE PURITY OF ASPIRIN

Requirements

Aspirin, sodium hydroxide, potassium hydrogen phthalate, phenolphthalein indicator and phenol red, etc.

Theory

The principle involved in the assay of aspirin is acid-base titration where the acidic group in aspirin is neutralized by titrating with base, i.e. NaOH and the excess base is back titrated with an acid (HCl) using phenol red as an indicator where the end point is pink to colourless.

Procedure

Standardization of 0.5 M NaOH

Weigh about 2.5 g of potassium hydrogen phthalate into 250 ml conical flask which is previously dried at 110°C. Dissolve the sample in about 30 ml of distilled water. Add five drops of phenolphthalein indicator and titrate with 0.5 M NaOH by constant swirling to the first appearance of a permanent pink color.

Each ml of 0.5 M NaOH is equivalent to 0.1021 g of $C_8H_5KO_4$.

Standardization of 0.5 M HCl

Pipette out 20 ml of 0.5 M NaOH solution into 250 ml conical flask and add five drops of phenolphthalein indicator and titrate with 0.5 M HCl by constant swirling to the disappearance of pink color.

Assay

Weigh accurately about 0.5 g of sample dissolved in 15 ml of ethanol (95%), add 50 ml of 0.5 M NaOH. Boil gently for 10 minutes, cool and titrate the excess alkali with 0.5 M HCl using phenol red as an indicator. Repeat the titration with blank.

Each ml of 0.5 M HCl is equivalent to 0.04504 g of $C_9H_7O_4$.

$$\% \text{ purity } = \frac{\text{Titre value} \times \text{molarity of HCl} \times \text{Eq. factor}}{\text{Weight of sample taken} \times \text{expected molarity}} \times 100$$

Result

The percentage purity of aspirin is found to be.

EXPERIMENT 11: TO DETERMINE PERCENTAGE PURITY OF IBUPROFEN

Requirements

Ibuprofen, sodium hydroxide, potassium hydrogen phthalate, phenolphthalein indicator, phenol red, etc.

Theory

The principle involved in the assay of ibuprofen is acid-base titration where the acidic group in ibuprofen is neutralized by titrating with base, i.e. NaOH using phenolphthalein as an indicator where the end point is colourless to pink.

Procedure

Standardization of 0.1 M NaOH

Weigh about 0.5 g of potassium hydrogen phthalate into 250 ml conical flask which is previously dried at 110°C. Dissolve the sample in about 30 ml of distilled water. Add five drops of phenolphthalein indicator and titrate with 0.1 M NaOH by constant swirling to the first appearance of a permanent pink color.

Each ml of 0.1 M NaOH is equivalent to 0.02042 g of $C_8H_5KO_4$.

Assay

Weigh accurately about 0.5 g of drug and dissolve in 100 ml of ethanol (95%) and titrate with a 0.1M NaOH using phenolphthalein as an indicator where the end point is permanent pink colour. Repeat the titration with blank.

Each ml of 0.1 M NaOH is equivalent to 0.02663 g of $C_{13}H_{18}O_2$.

$$\% \text{ purity } = \frac{\text{Titre value} \times \text{molarity of NaOH} \times \text{Eq. factor}}{\text{Weight of sample taken} \times \text{expected molarity}} \times 100$$

Result

The percentage purity of ibuprofen is found to be ...

EXPERIMENT 12: TO DETERMINE PERCENTAGE PURITY OF SULPHAMETHOXAZOLE

Requirements

Sulphamethoxazole, sulphanilic acid, sodium nitrite, potassium bromide, hydrochloric acid, starch iodide external indicator.

Principle

The principle involoved in the assay of sulphamethoxazole is diazotization where the Sodium nitrite consumed by sulphamethoxazole to form diazonium salt is calculated by using starch iodide as an external indicator which gives blue colour as an end point.

Procedure

Standardization of 0.1 M $NaNO_2$

Weigh about 0.3 g of sulphanilic acid and dissolve in 50 ml of 2M HCl. Add 3 g of potassium bromide, cool in ice and titrate with 0.1M $NaNO_2$ solution using starch iodide as an external indicator which gives blue colour as an end point.

Each ml of 0.1 M $NaNO_2$ is equivalent to 0.01732 g of H_2SO_4.

Assay

Weigh accurately about 0.2 g of sample dissolved in 50 ml of 2M HCl. Add 3 g of potassium bromide, cool in ice and titrate against 0.1 M $NaNO_2$ using starch iodide as an indicator. Repeat the titration with blank.

Each ml of 0.1M $NaNO_2$ is equivalent to 0.02533 g of $C_{10}H_{11}N_3O_3S$.

$$\% \text{ purity} = \frac{\text{Titre value} \times \text{molarity of NaNO}_2 \times \text{Eq. factor}}{\text{Weight of sample taken} \times \text{expected molarity}} \times 100$$

Result

The percentage purity of sulphamethoxazole is found to be ...

EXPERIMENT 13: TO DETERMINE PERCENTAGE PURITY OF FRUSEMIDE

Requirements

Frusemide, frusemide tablets, dimethylformamide, sodium hydroxide and bromothymol blue.

Assay

Weigh accurately about 0.5 g of sample dissolve in 40 ml of dimethylformamide and titrate with 0.1 M sodium hydroxide using bromothymol blue as an indicator. Repeat the titration with blank.

Each ml of 0.1 M sodium hydroxide is equivalent to 0.03307 g of $C_{12.}H_{11}ClN_2O_2S$.

For Frusemide Tablets

Weigh and powder 20 tablets. Weigh a quantity of the powder containing 0.1 g of frusemide and shake with 150 ml of 0.1 M sodium hydroxide for 10 minutes. Add sufficient 0.1 M sodium hydroxide to produce 250 ml and filter. Dilute 5 ml to 200 ml with 0.1 M sodium hydroxide and measure the absorbance of the resulting solution at the maximum at about 271 nm. Calculate the content of $C_{12.}H_{11}ClN_2O_2S$, taking 580 as the specific absorbance at 271 nm.

Result

The percentage purity of frusemide is found to be.

EXPERIMENT 14: TO DETERMINE PERCENTAGE PURITY OF ATROPINE SULPHATE

Requirements

Atropine sulphate, anhydrous glacial acetic acid and perchloric acid.

Assay

Weigh accurately about 0.5 g of sample dissolve in 30 ml of anhydrous glacial acetic acid. Titrate with 0.1 M perchloric acid, determining the end point potentiometrically. Carry out a blank titration.

Each ml of 0.1 M perchloric acid is equivalent to 0.06768 g of $(C_{17}H_{23}NO_3)_2H_2SO_4$.

Result

The percentage purity of atropine sulphate is found to be ...

EXPERIMENT 15: TO DETERMINE PERCENTAGE PURITY OF PHENOBARBITONE

Requirements

Phenobarbitone, pyridine, thymolphthalein, ethanol and sodium hydroxide.

Assay

Dissolve 0.1 g of sample dissolve in 5 ml of pyridine, add 0.25 ml of thymolphthalein solution and titrate with 0.1 M ethanolic sodium hydroxide until a purple blue colour is obtained. Repeat the titration without the substance under examination. The difference between the titrations represents the amount of sodium hydroxide required.

Each ml of 0.1 M ethanolic sodium hydroxide is equivalent to 0.01161 g of $C_{12}H_{12}N_2O_3$

Result

The percentage purity of phenobarbitone is found to be ...

EXPERIMENT 16: TO DETERMINE PERCENTAGE PURITY OF CHLOROQUINE SULPHATE

Requirements

Chloroquine sulphate, anhydrous glacial acetic acid and perchloric acid.

Assay

Weigh accurately about 0.5 g of sample dissolve in 50 ml of anhydrous glacial acetic acid. Titrate with 0.1 M perchloric acid, determining the end point potentiometrically. Carry out a blank titration.

Each ml of 0.1 M perchloric acid is equivalent to 0.0418 g of $C_{18}H_{26}ClN_3\cdot H_2SO_4$

Result

The percentage purity of chloroquine sulphate is found to be ...

EXPERIMENT 17: TO DETERMINE PERCENTAGE PURITY OF CHLORPROMAZINE HYDROCHLORIDE

Requirements

Chlorpromazine hydrochloride, acetone of mercuric acetate, perchloric acid and methyl orange.

Assay

Weigh accurately about 0.6 g of sample dissolve in 200 ml of acetone and add 15 ml of mercuric acetate solution. Titrate with 0.1 M perchloric acid using a saturated solution of methyl orange as indicator. Carry out a blank titration.

Each ml of 0.1 M perchloric acid is equivalent to 0.03553 g of $C_{17}H_{19}ClN_2S{\cdot}HCl$.

Result

The percentage purity of chlorpromazine hydrochloride is found to be ...

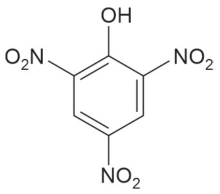
EXPERIMENT 18: TO PREPARE AND SUBMIT PICRIC ACID (2,4,6-TRINITROPHENOL) FROM PHENOL (NITRATION)

Requirements

Phenol, conc. H_2SO_4, conc. nitric acid and ethanol, water.

Theory

Chemical formula: $C_6H_3N_3O_7$
Molecular weight: 229
Melting point: 122 °C
Chemical name: 2,4,6-trinitrophenol (TNP)



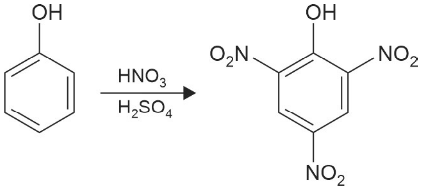
Picric acid is 2,4,6-trinitrophenol. Picric acid is available in yellow crystalline solid and is one of the most acidic phenols. It is used as tropical anti-infective and disinfectant so that used as a cleaning agent and also preservative due to presence of phenol. Picric acid is obtained by nitrating phenol. In pharmacology experiments, picric acid is also used to mark the rats and mice.

Nitration

Nitration is an example of electrophilic aromatic substitution reaction. A large number of aromatic compounds can be easily nitrated. Phenols are easily nitrated by using nitrating mixture. The reaction is vigorous and sometimes violent. The hydrogen atom is replaced by nitro group. The nitration of aromatic compounds is usually done by using conc. HNO_3 in presence of conc. H_2SO_4. Nitration of aromatic compounds is an example of electrophillic aromatic substitution. H_2SO_4 not only provides strong acedic medium but it also converts the HNO_3 into reactive electrophile nitronium ion $(NO^{+}{}_{2})$ which attacks the aromatic ring.

Nitration is usually carried out at low temperature. At high temperature there is loss of material due to oxidation by HNO_3. Phenol being an activated nucleus towards electrophillic aromatic substitution, the nitration reaction occurs very easily. It undergoes nitration with HNO_3 even at room temperature forming ortho and para nitrophenol which can be separated by steam distillation. Phenol when treated with conc. HNO_3 in presence of conc. H_2SO_4 undergoes nitration at both ortho and para position to yield picric acid. It is better if phenol is first converted into phenol sulphonic acid by treatment with H_2SO_4 and then nitrated with conc. HNO_3.

Chemical Reaction



2,4,6-Trimitrophenol

Mechanism

The nitration of phenol by concentrated nitric acid in presence of sulphuric acid (conc.) is electrophallic aromatic substitution which involves generation of nitronium ion by reaction of nitric acid with sulphuric acid, which in turn attack on p-position of aromatic ring of phenol in reaction and then this positively charged aromatic ring intermediate reacts with HSO_4^- (which is generated in reaction) immediately to give p-substituted Phenol, which again attacked by nitronium ion to get disubstituted phenol and this disubstituted phenol again goes for various steps to get trisubstituted phenol, i.e. 2,4,6-trinitrophenol (picric acid).

Physical Properties

It is a yellow, crystalline solid, MP 122°C, with bitter taste (picro-bitter).

Uses

It is used for the identification of aromatic hydrocarbons, amines, detection of K in presence of sodium. It is used as explosives, in matches, textile and leather industry.

Chemicals Required

1. Phenol	8 g
2. Sulphuric acid	10 ml
3. Nitric acid	30 ml

Procedure

1. Clean the glassware's with chromic acid wash dry with acetone/methanol in oven.
2. Take 8 g of phenol in dry round bottom flask; to this add 10 ml (18.5 g) of concentrated sulphuric acid. Shake the mixture, which becomes warm because the reaction is exothermic.
3. Heat the flask on boiling water both for 30 minutes to complete the formation of phenol sulphonic acid. Cool to room temperature to get viscous syrup.

4. Place the flask in fuming cupboard and add 30 ml conc. nitric acid dropwise with constant shaking, mix and allow the mixture to stand undisturbed usually within 1 minute a vigorous (but harmless) reaction occurs and red fumes generated complete this action till all nitric acid is added.
5. Heat the flask for one and half hour with occasional shaking. Drying this heavy oil ultimately forms a mass of crystals.
6. Add 100 ml of cold water mix well and then chill thoroughly in ice water filter yellow crystal at pump, wash with water toll free from acid.
7. Recrystallize from mixture of 1 volume of ethanol and 2 volume of water, take 90 ml of mixture to get pale yellow leaflet of picric acid having.

Result

Picric acid is prepared and submitted.

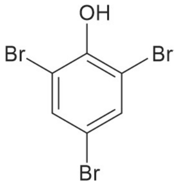
EXPERIMENT 19: TO PREPARE AND SUBMIT 2,4,6-TRIBROMOPHENOL (BROMINATION)

Requirements

Phenol, bromine, ice water and rectified spirit.

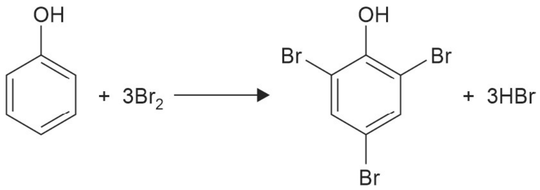
Theory

Chemical formula: $C_6H_3Br_3O$
Molecular weight: 330.8
Melting point: 95°C
Chemical name: 2,4,6-tribromophenol (TBP)



2,4,6-tribromophenol (TBP) is a brominated derivative of phenol. It is used as a fungicide, as a wood preservative, and an intermediate in the preparation of flame retardants. Although natural TBP has been identified in ocean sediments as a metabolite of marine fauna, the commercial product is prepared industrially. The predominant use of TBP is as an intermediate in the preparation of flame retardants such as brominated epoxy resins. TBP is reacted with sodium hydroxide to form the sodium salt, which is used as a fungicide and wood preservative. The bismuth salt is the active ingredient in Xeroform dressing. Microbial metabolism in products treated with TBP is known to produce 2,4,6-tribromoanisole. TBP can be prepared by the controlled reaction of elemental bromine with phenol:

Chemical Reaction



Chemicals Required

Phenol	5 g
Bromine	8 ml

Procedure

1. Dissolve 5 g of phenol in small amount of water and add 8 ml of bromine solution dropwise with continous shaking.
2. Pour the reaction mixture into ice cold water.
3. Filter the crude product and wash well with water.
4. Recrystallize from dilute ethanol to yield 2,4,6-tribromophenol as colorless crystalline material.

Result

2,4,6-tribromophenol is prepared and submitted.

EXPERIMENT 20: TO PREPARE AND SUBMIT METHYL ORANGE FROM SULPHANILIC ACID

Requirements

Anhydrous sodium carbonate, sulphanilic acid, sodium nitrite, hydrochloric acid, and dimethylaniline.

Theory

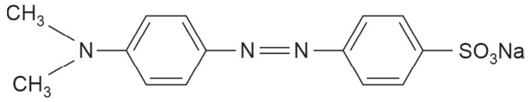
Chemical formula: $C_{14}H_{14}N_3O_3SNa$

Molecular weight: 327.33

Melting point: 300°C

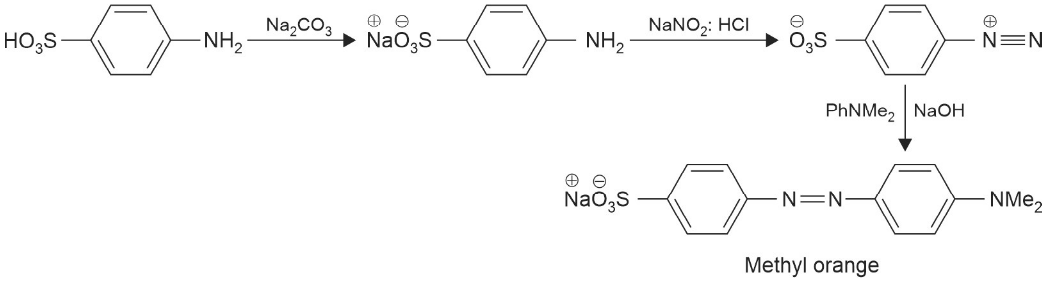
Chemical name: 4 [(4-dimethylamino) phanylazo] benzene sulphonic acid p-dimethylamino benzene sulphonate

Methyl orange is a pH indicator frequently used in titrations. It is often used in titrations because of its clear colour change. Because it changes colour at the pH of a mid-strength acid, it is usually used in titrations for acids. Unlike a universal indicator, methyl orange does not have a full spectrum of colour change, but has a sharper end point. Methyl orange is an example of acid-base indicator, which is widely use to locate the end-point in acidimetry and alkalimetry. The colour change of indicator is yellow to red.



In laboratory it is prepared from sulphanilic acid sodium nitrite and dimethylaniline.

Chemical Reaction



Methyl orange

Physical Properties

Orange yellow powder or crystals soluble in 500 parts of water more soluble in hot water practically insoluble in alcohol.

Uses

Methyl orange is mainly used as an indicator.

Chemicals Required

1. Sulphanillic acid	7 g
2. Sodium carbonate	2 g
3. Sodium nitrite	2.2 g
4. Hydrochloric acid	12 ml
5. Dimethylaniline	4 ml
6. Sodium hydroxide	10%

Procedure

1. Dissolve 7 g of finely powdered sulphanilic acid and 2 g of anhydrous sodium carbonate in 50 ml of water contained in a beaker.
2. Warm the mixture gently in order to obtain a clear solution.
3. Add a solution of sodium nitrite (2.2 g in 10 ml of water) and then cool the mixture in ice-water until the temperature has fallen to 5°C.
4. Add 8 ml of concentrated hydrochloric acid to the above mixture very slowly and with constant mixing.
5. When all the acid has been added allow the contents to stand in ice-water for 15 minutes to ensure complete diazotisation (during this period fine crystals of the internal salt separate from the pink solution).
6. Dissolve 4 ml of dimethylaniline in a mixture of 4 ml of conc. HCl and 10 ml of water.
7. Cool the solution in ice water and add it slowly to the cold well-stirred diazo solution (pale red colouration is developed).
8. Allow the mixture to stand for 5 minutes and then slowly with stirring added aqueous 10% sodium hydroxide solution until the mixture attains a uniform orange colour to get sodium salt of methyl orange.
9. The sodium salt of methyl orange separates as very fine particles warm the mixture to 50–55°C to enhance the particle size.
10. Now cool the mixture for 10–15 minutes and then cool in ice-water filter off the methyl orange.
11. Add the pump drain thoroughly and recrystallize the methyl orange from about 100 ml of boiling water.

Result

Methyl orange is prepared and submitted.

EXPERIMENT 21: TO PREPARE AND SUBMIT METHYL RED

Requirements

Anthranilic acid, conc. HCl, sodium nitrite, sodium acetate, sodium hydroxide, acetic acid, methyl alcohol, toluene, N and N-dimethylaniline.

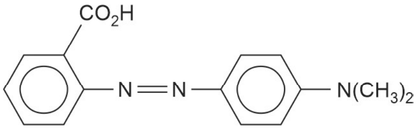
Theory

Chemical formula: $C_{15}H_{15}N_3O_2$

Molecular weight: 269.3

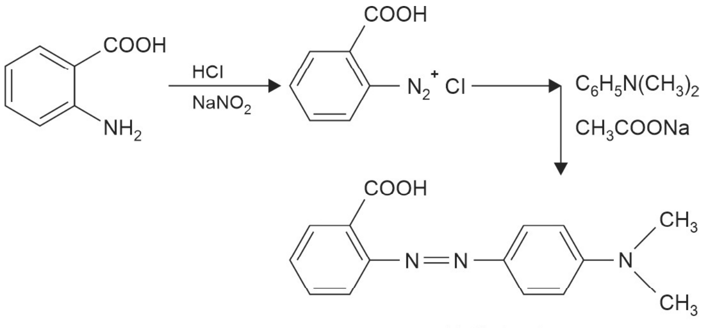
Melting point: 181–182°C

Chemical name: 2-[(4-(dimethylanines-phenyl]azo] benzoic acid (o-carboxybenzene-azo-dimethylaniline)



Methyl red is an indicator dye that turns red in acidic solutions. It is an azo dye and is a dark red crystalline powder. Methyl red is an example of acid-base indicator and is widely used for the location of end point in acidimetry and alkalimetry. The colour change of this indicator is red to yellow (pH range is 4.2–6). The methyl red test is used to identify enteric bacteria based on their pattern of glucose metabolism. These bacteria are called methyl-red positive and include *Escherichia coli* and *Proteus vulgaris*. As an azo dye, methyl Red may be prepared by diazotization of anthranilic acid, followed by reaction with dimethylaniline.

Chemical Reaction



Methyl red

Procedure

1. Dissolve 2.2 g of pure anthranilic acid in a mixture of 1.7 ml of conc. HCl and 5 ml of water using gentle heating.
2. Remove the insoluble impurities by filtration and transfer the contents to 250 ml beaker surrounded by ice bath.
3. Add 10 g of crushed ice and 2.5 ml of conc. HCl and stir continuously. When the temperature falls to about 3°C slowly added a cold solution of 1.2 g of sodium nitrite in 2.5 ml of water. Keep the temperature between 3–5°C until the diazotization reaction completes.
4. Add 3.0 ml of pure dimethylaniline to the above diazosolution while maintaining the temperature about 5°C. Dissolve 2.3 g of sodium acetate in 3 ml of water and add this solution to the above solution.
5. Allow the mixture to stay in ice bath for 1 hour with occasional mixing and allow the temperature to reach that of room temperature.

6. Add 1.5 ml of 20% w/v sodium hydroxide solution and allow to stand for 1 hour.
7. Filter the contents at pump drain thoroughly. Add 3 ml of acetic acid (10%) to remove the dimethyl aniline and wash with water again.
8. Drain the product thoroughly and dry in between sheets of filter paper.

Result

Methyl red is prepared and submitted.

EXPERIMENT 22: TO PREPARE AND SUBMIT PHENOLPHTHALEIN FROM PHENOL

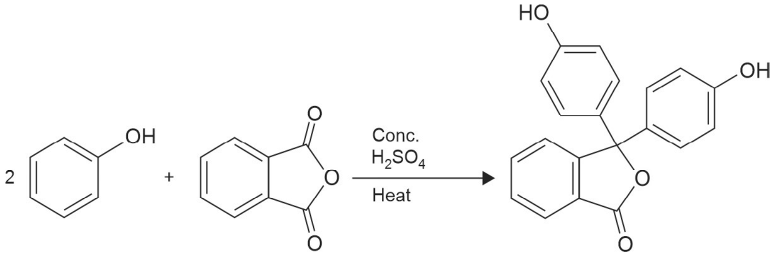
Requirement

Phenol, phthalic anhydride, concentrated sulphuric acid, sodium hydroxide and acetic acid.

Principle

Synthesis: Phenolphthalein can be synthesized by condensation of phthalic anhydride with two equivalents of phenol under acidic conditions. Phenolphthalein's common use is as an indicator in acid-base titrations. It also serves as a component of universal indicator, together with methyl red, bromothymol blue, and thymol blue. Phenolphthalein has been used for over a century as a laxative, but is now being removed from over-the-counter laxatives because of concerns over carcinogenicity

Reaction



The reaction can also be catalyzed by a mixture of zinc chloride and thionyl chloride.

Procedure

1. Take 18.8 g. of phenol with 14.8 g of phthalic anhydride in a round bottom flask.
2. Heat the mixture on an oil bath till the contents melts.
3. Slowly add 8 ml of concentrated sulphuric acid and heat the reaction mixture on an oil bath at 120°C for 6 hours until the contents becomes semi solid and dark red in colour.
4. Pour the reaction mixture in 500 ml hot water and boil until the colour of the phenol disappears.
5. Filter the solid mass, wash with water then dissolve in minimum quantity of NaOH solution, filter off any solid material.
6. Acidify the filtrate with dilute acetic acid and few drops of hydrochloric acid.
7. Allow to stand for some time.
8. Filter the yellow granules of phenolphthalein and recrystallize from ethanol.
   Melting point: 256–258°C

Calculation

$$\text{Practical yield} = \text{......}\ g$$
$$\text{Theoretical yield} = 6\ g$$
$$\%\ \text{yield} = \frac{\text{Theoretical value}}{\text{Practical value}} \times 100$$
$$\%\ \text{yield} = \text{......}\ \%$$

Result

Phenolphthalein is synthesized and the percentage (%) yield is found to be ...... %.

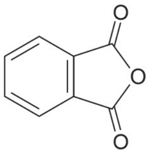
EXPERIMENT 23: TO PREPARE AND SUBMIT PHTHALIC ANHYDRIDE

Requirement

Phthalic acid.

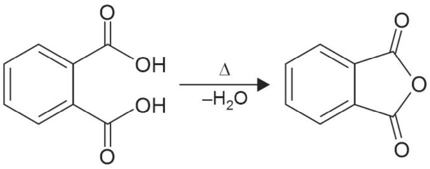
Theory

Chemical formula: $C_8H_4O_3$
Molecular weight: 148
Melting point: 131°C
Chemical name: 2-Benzofuran-1,3-dione/Isobenzofuran-1,3-dione



Phthalic anhydride is prepared from naphthalene by oxidation with a mixture of $HgSO_4$ and $CuSO_4$ in presence of H_2SO_4. By passing naphthalene and oxygen over suitable catalyst at 400–500°C. Phthalic acid when heated at 160°C, it loses molecule of water to form phthalic anhydride.

Chemical Reaction



Uses

Manufacture of phthalins, phthalates, benzoic acid synthetic indigo, artificial resins.

Chemicals Required

Phthalic acid	5 g

Procedure

1. Heat the soda bath at temperature about 250°C.
2. Pour phthalic acid in China dish and cover with a paper having holes.

3. Keep plugged with cotton in stem as upside down a china dish with paper.
4. Keep this assembly on the soda bath.
5. Needle shaped crystals of phthalic anhydrides are obtained in filter paper.

Result

Phthalic anhydride is prepared and submitted.

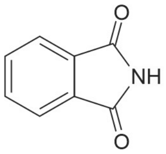
EXPERIMENT 24: TO PREPARE AND SUBMIT PHTHALIMIDE FROM PHTHALIC ANHYDRIDE

Requirements

Phthalic anhydride, urea and alcohol.

Theory

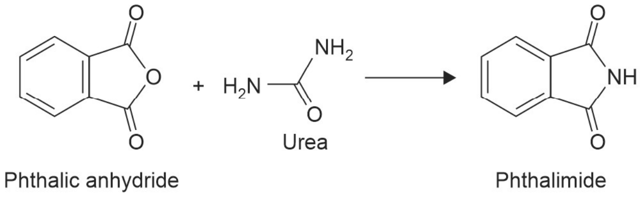
Chemical formula: $C_8H_5NO_2$
Molecular weight: 147.13
Melting point: 310 °C
Chemical name: Isoindole-1,3-dione



Theory

Phthalimide, derived from phthalic anhydride with ammonium hydroxide by heating, is used in the synthesis of primary amines and amino acids. It is used to make synthetic indigo and phthalocyanine pigments which have macrocyclic structure showing striking coloring features like porphyrins (biopigments). Phthalimide has isoindole moiety. Phthalimide is an imide, which is a chemical compound with two carbonyl groups bound to a primary amine or ammonia. It is a white solid at room temperature. Phthalimide is used in plastics, in chemical synthesis, and in research. It can also be prepared by reacting dry phthalic anhydride with dry urea at their melting print. This is called fusion reaction.

Chemical Reaction



Chemicals Required

1. Phthalic acid	10 g
2. Urea	2 g
3. Water	25 ml

Procedure

1. Mix intimately 5 g of phthalic anhydride and 1 g of urea and place this mixture in a flask.
2. Heat the flask to 130–135°C on a sand bath up to 15 minutes.
3. When mixture froths and become solid cold content at room temperature and then add nearly 5 ml of water.
4. Stir the content well and filter the product.
5. Wash with a little amount of water and recrystallized from alcohol.

Result

Phthalimide is prepared and submitted.

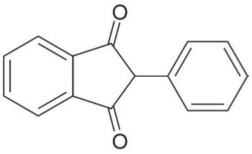
EXPERIMENT 25: SYNTHESIS AND CHARACTERIZATION OF PHENINDIONE

Requirements

Phthalic anhydride: 5 g, ethanol: 7 ml, sodium acetate: 0.5 g, acetic acid: 0.5 ml and phenyl acetic acid: 4.5 g.

Theory

Phenindione is an anticoagulant which functions as a vitamin K antagonist. Phenindione thins the blood by antagonizing vitamin K which is required for the production of clotting factors in the liver. Anticoagulants such as phenindione have no direct effect on an established thrombus, nor do they reverse ischemic tissue damage.



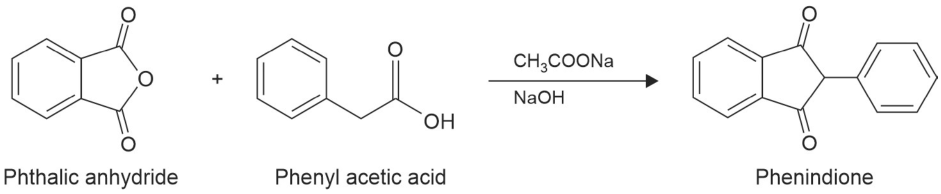
IUPAC name: 2-phenyl-1*H*-indene-1,3(2*H*)-dione

Procedure

1. In a 250 ml round bottom flask, take 5 g of phthalic anhydride and dissolve in 7 ml of ethanol.
2. Then add 0.5 g of sodium acetate and 0.5 ml of acetic acid. Then slowly add 4.5 g of phenyl acetic acid.
3. The solution is then refluxed for 2 hours.
4. Allow to cool and make the solution alkaline by adding 5% NaOH solution.
5. Filter and dry the product for characterization.

Theoretical Yield

The theoretical yield may be calculated from the equation:



148 g of phthalic anhydride after reacting with phenyl acetic acid yields phenindione = 221 g

5 g of phthalic anhydride shall yield phenindione = $\frac{221}{448} \times 5 = 7.46$ g

Hence, theoretical yield of phenindione = **7.46 g**

Characterization

Physical appearance: White crystalline powder
Melting point: 150°C
UV: 254 nm
Solubility: Very slightly soluble in water
TLC solvent: Ethyl acetate: n-hexane (1:1)

Result

Phenin dione is prepared and submitted.

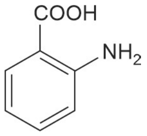
EXPERIMENT 26: TO PREPARE AND SUBMIT ANTHRANILLIC ACID

Requirements

Phthalimide, NaOH, bromine solution, glacial acetic acid and decolorizing carbon.

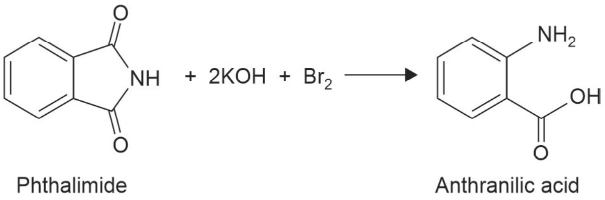
Theory

Chemical formula: $C_7H_7NO_2$
Molecular weight: 137.14
Melting point: 145°C
Chemical name: *o*-Amino benzoic acid



Anthranillic acid, amino derivative of benzoic acid, may be conveniently prepared by the action of sodium hypobromite solution on phthalimide in alkaline solution at 80°C. The ring in phthalimide is opened by hydrolysis to anthranilic acid and the latter undergoes the Hoffmann reaction. The compound is consequently amphoteric. In appearance, anthranilic acid is a white solid when pure, although commercial samples may appear yellow. It is sometimes referred to as vitamin L_1 and has a sweetish taste. Cadmium salt has been used as an ascaricide in swine. Anthranilic acid can be used in organic synthesis to generate benzyne.

Chemical Reaction



Chemicals Required

1. Phthalimide	6 g
2. Sodium hydroxide	2.1 ml
3. Potassium hydroxide (10%)	20 ml
4. Bromine solution	4.2 ml
5. Glacial acetic acid	5 ml
6. Decolorizing carbon	qs

Procedure

1. Dissolve 7.5 g NaOH in 40 ml water and cool in an ice bath to about 0°C
2. Add 2.1 ml Br_2 solution to it.
3. To this solution add 6 g of phthalimide and 20 ml 10% KOH solution.
4. Heat the solution for 5–10 minutes till phthalimide dissolves.
5. Filter the solution and neutralize the solution with glacial acetic acid.
6. Filter the solid crystals if anthranilic acid, wash with water.
7. Recrystallize from hot water with the addition of a little decolorizing carbon.
8. Collect the acid on a Buchner funnel and dry at 100°C.

Result

Anthranilic acid is prepared and submitted.

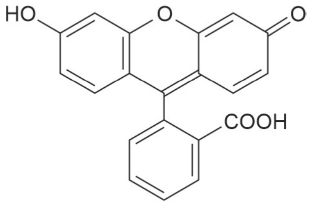
EXPERIMENT 27: TO PREPARE AND SUBMIT FLUORESCEIN (FRIEDEL-CRAFTS REACTION)

Requirements

Phthalic anhydride, resorcinol, anhydrous zinc chloride and conc. HCl

Theory

Chemical formula: $C_{20}H_{12}O_5$
Molecular weight: 332.31
Melting point: 314°C
Boiling point: 620°C
Chemical name: Resorcinol phthalein, diresorcinol phthalein, tetraoxyphthalophenone anhydride



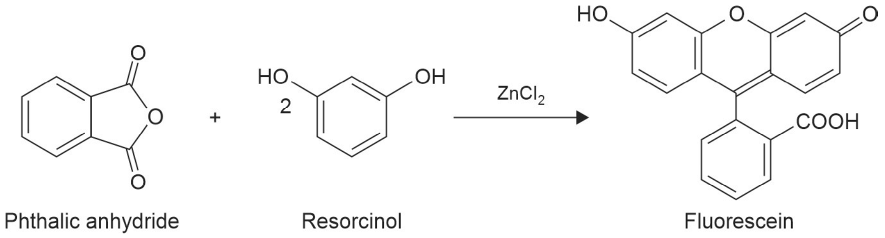
Fluorescein

Fluorescein ($C_{20}H_{12}O_5$) is a synthetic organic compound available as a dark orange/red powder soluble in water and alcohol. It is widely used as a fluorescent tracer for many applications. Fluorescein is a fluorophore commonly used in microscopy, in a type of dye laser as the gain medium, in forensics and serology to detect latent blood stains, and in dye tracing. The major derivative is fluorescein isothiocyanate.

The color of its aqueous solution varies from green to orange as a function of the way it is observed: by reflection or by transmission, as it can be noticed in bubble levels in which fluorescein is added as a colorant to the alcohol filling the tube to increase the visibility of the air bubble and the precision of the instrument.

Fluorescein can be prepared from phthalic anhydride and resorcinol in the presence of zinc chloride via the **Friedel-Crafts reaction.**

Chemical Reaction



Chemicals Required

Phthalic anhydride	7.5 g
Resorcinol	12 g
Anhydrous zinc chloride	5 g
Conc. HCl	8 ml

Procedure

1. Grind accurately 7.5 g of phthalic anhydride and 12 g of resorcinol and powder very finely.
2. Transfer the contents to a 250 ml conical flask and heat on a sand-bath at 180°C.
3. Add 5 g of anhydrous zinc chloride to the above mixture in small portion with constant stirring.
4. Continue to heat until the contents turn dark and becomes viscous.
5. Cool the mixture to 90°C and add 100 ml of water and 8 ml of conc. HCl.
6. Filter the contents and dry the filtrate to get the product.
7. Purify by dissolving it in dilute sodium hydroxide solution and precipitating with dilute hydrochloric acid.
8. Wash and dry at 100 °C.

Result

Fluorescein is prepared and submitted.

EXPERIMENT 28: TO PREPARE AND SUBMIT ANILINE

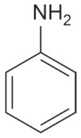
Requirement

Nitrobenzene, HCl, tin granules, sodium hydroxide, common salt.

Theory

Chemical formula: C_6H_7N
Molecular weight: 93.13

Boiling point: 184 ºC
Chemical name: Benzamine, phenylamine, aminobezene, aminophen

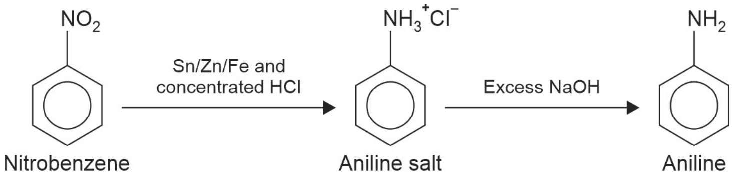


Aniline also known as phenylamine, an aromatic amine, is prepared by reduction of nitrobenzene with as a catalyst in gaseous phase. It is a colourless liquid. Its boiling point is 184ºC, it has a paint characteristic odour. It is sparingly soluble in the water but readily soluble in ethanol, ether and chloroform.

Nitrobenzene is reduced to phenylammonium ions using a mixture of tin and concentrated hydrochloric acid. The mixture is heated under reflux in a boiling water bath for about half an hour. Under the acidic conditions, rather than getting phenylamine directly, we will get phenylammonium ions. The nitrobenzene has been reduced by gaining electrons in the presence of the acid. Sodium hydroxide solution is added to the product of the first stage of the reaction.

The phenylamine is formed together with a complicated mixture of tin compounds from reactions between the sodium hydroxide solution and the complex tin ions formed during the first stage. The phenylamine is finally separated from this mixture. The separation is long, tedious and involving steam distillation, solvent extraction and a final distillation.

Chemical Reaction



Uses

Manufacture of dyes, production of antioxidants and sulpha drugs, resins, varnishes, vulcanizing rubber as solvent. For making isocyanates required for polyurethane plastics used for insulation.

Chemicals Required

1. Nitro benzene	21 ml
2. Tin granules	5 g
3. Hydrochloric acid	100 ml
4. Sodium hydroxide	75 g
5. Common salt	30 g

Procedure

1. Place 21 ml nitrobenzene and 5 g of tin granules in 250 ml round bottom flask fitted with water reflux condenser.
2. Pour 20 ml of HCl down the condenser if temperature of the mixture is hot. Keep cool by immersing in water bath.

3. Repeat step 2 till 100 ml HCl has been added and heat the flask water bath for half an hour till the odour of nitrobenzene ceases and reduction is compete.
4. Cool the flask and add solution of 75 g NaOH in 100 ml water solution strongly alkaline to liberate aniline.
5. Transfer the flask liquid to steam distillation assembly do the steam distillation of aniline.
6. To the distillate add common salt and separate colorless by separately.

Result

Aniline is prepared and submitted.

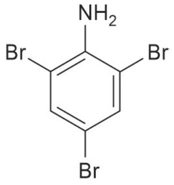
EXPERIMENT 29: TO PREPARE AND SUBMIT 2,4,6-TRIBROMOANILINE FROM ANILINE (BROMINATION)

Requirements

Aniline, glacial acetic acid, bromine, rectified spirit.

Theory

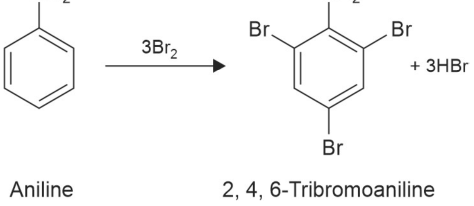
Chemical formula: $C_6H_4Br_3N$
Molecular weight: 329.83
Melting point: 119–122°C
Boiling point: 300°C
Chemical name: 2,4,6 tribromoaniline



Theory

Aniline is the starting material in the dye manufacturing industry. Aromatic amines are weaker bases reacting with strong acids to form amides. 2,4,6-Tribromoaniline ($Br_3C_6H_2NH_2$) is a chemical compound which has a strong activating amino group. Aniline undergoes nucleophilic substitution with bromine. Aniline on treatment with bromine readily undergoes substitution at both the ortho and para positions to yield 2,4,6-tribromoaniline. The presence of bromine atoms in tribromoaniline, reduces the basic properties of the amino group and salts even with strong acids are almost completely hydrolyzed in presence of water. It has white crystals, soluble in ether, chloroform, alcohol.

Chemical Reaction



Chemicals Required

Aniline	5 ml
Glacial acetic acid	40 ml
Bromine	8.5 ml

Procedure

1. Take 5 ml of aniline in 20 ml of glacial acetic acid in a conical flask.
2. Add 8.5 ml of bromine in 20 ml glacial acetic acid.
3. Cautiously add bromine solution drop wise from separating funnel to aniline solution with constant shaking.
4. Cooled in ice bath.
5. Allow the mixture to stand for 15–20 min.
6. Pour into 50–100 ml of water, filter off the bromo compound and wash with a little cold water.
7. Recrystallise from dilute ethanol.
8. Calculate the final yield of the product.

Theoretical Calculation

93.13 g of aniline gives 329.81 g of tribromoaniline
1 g of aniline will form X g of tribromoaniline

Theoretical yield = ... g
Practical yield = ... g

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

% yield = ... %

Result

2,4,6-tribromoaniline is prepared and submitted.

EXPERIMENT 30: TO PREPARE AND SUBMIT SULFANILIC ACID

Requirement

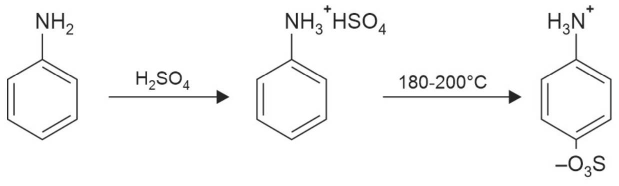
Aniline, sulphuric acid.

Theory

Chemical formula: $C_6H_7NO_3S$
Molecular weight: 173.19
Melting point: 288°C
Chemical name: 4-Aminobenzene sulfonic acid and p-aniline sulfonic acid

It is readily prepared from aniline and sulphuric acid. Aniline is usually sulfonated by 'baking' the salt, anilinium hydrogen sulfate, at 180–190°C; the chief product is the para isomer. Sulfonation is known to be reversible.

Chemical Reaction



Anilinium hydrogen sulphate Sulfanilic acid

Physical Properties

Sulfanilic acid is insoluble is all organic solvent and also insoluble in water. Sulfanilic acid is soluble in aqueous bases but insoluble in mineral acid. Orthorhombic plates from water, become anhydrous at 100°C.

Chemicals Required

Aniline	10 ml
Sulphuric acid	20 ml

Procedure

1. Place 10 ml of aniline in 250 ml conical flask.
2. Add slowly 20 ml of concentrated sulphuric acid and slake vigorously.
3. Heat the solution in oil both at 180–200°C for 1 hour in a fuming cupboard.
4. Cool and pour carefully in 100 ml of cold water with stirring.
5. Filter off sulfanilic acid.

Result

Sulfanilic acid is prepared and submitted.

EXPERIMENT 31: SYNTHESIS AND CHARACTERIZATION OF SULPHANILAMIDE

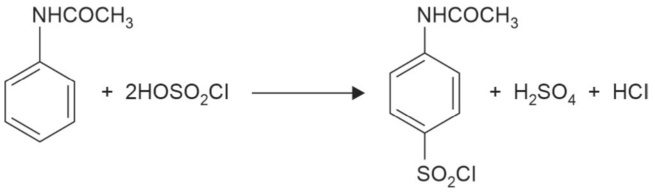
Requirements

Acetanilide: 25 g, chlorosulphonic acid: 63 ml, aqueous ammonia: 120 ml

Theory

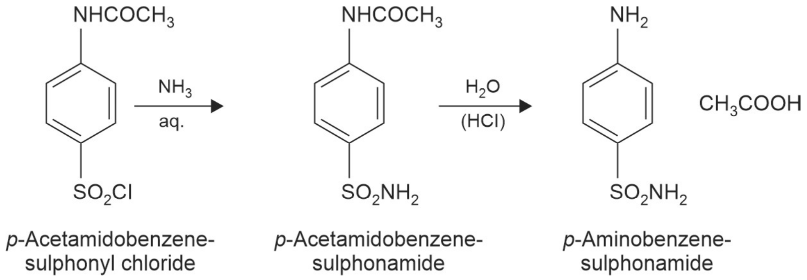
The synthesis of this important compound may be accomplished by the following series of reactions:

a. Treatment of acetanilide with excess of chlorosulphonic acid affords *p*-acetamidobenzenesulphonyl chloride–a solid, mp 149°C:



b. This is converted by aqueous ammonia into *p*-acetamidobenzene sulphonamide; the pure compound has mp 218°.

c. By boiling with dilute hydrochloric acid the protecting acetyl group is removed without hydrolyzing the sulphonamido group. The liberated sulphonamide passes into solution as the hydrochloride, and the free base (*p*-aminobenzene sulphonamide) is obtained by neutralization with sodium bicarbonate or aqueous ammonia.



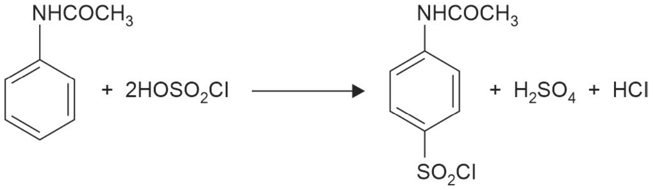
Procedure

p-Acetamidobenzenesulphonyl chloride:

Reaction A: Carefully add 25 g of dry powdered acetanilide, with occasional shaking, to 63 ml of chlorosulphonic acid contained in a 250 ml conical flask (fume-cupboard), and then heat the solution to 60–70°C for 2 hours. Cool the mixture and pour it *carefully* on to about 500 g of crushed ice, whereupon the sulphonyl chloride separates as a white solid. Filter off the sulphonyl chloride at the pump; wash it thoroughly with water, and drain. This crude product is sufficiently pure to use directly in the next stage. A small sample may be dried and recrystallized from chloroform, and is finally obtained as colourless crystals, mp 149–150°C.

Theoretical Yield

Reaction A: The theoretical yield is usually calculated from the equation under theory:



135 g of acetanilide on reacting with chlorosulphonic acid yields *p*-acetamido benzenesulphonyl chloride = 233.5 g

∴ 25 g of acetanilide shall yield *p*-acetamidobenzenesulphonyl chloride

$$= \frac{233.5}{135} \times 25 = 43.24 \text{ g}$$

Hence, theoretical yield of *p*-acetamidobenzenesulphonyl chloride = **43.24 g**

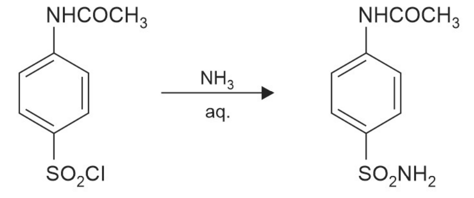
p-Acetamidobenzene sulphonamide:

Reaction B: Place the above crude damp sulphonyl chloride in a 500 ml conical flask and *cautiously* add 120 ml of concentrated ammonia solution (fume-cupboard): A vigorous reaction with evolution of heat will follow. Stir the mixture until a smooth thin paste is obtained and then heat at 70°C for 30 minutes with occasional stirring. Cool the mixture and make it just acid with dilute sulphuric acid. Filter off the precipitated *p*-acetamidobenzenesulphonamide at the pump, wash it well with cold water, and drain it thoroughly.

(yield almost theoretical.) Again, this material is pure enough for the next stage: a sample may be recrystallized from hot water and the pure sulphonamide obtained as colourless crystals, mp 219°C.

Theoretical Yield

Reaction B: The theoretical yield is usually calculated from the equation under theory:



p-Acetamidobenzene-sulphonyl chloride

p-Acetamidobenzene-sulphonamide

233.5 g of *p*-acetamidobenzenesulphonyl chloride on reacting with ammonia solution yields *p*-acetamidobenzene sulphonamide = 214 g

∴ 38 g of *p*-acetamidobenzenesulphonyl chloride shall yield *p*-acetamidobenzene sulphonamide

$$= \frac{214}{233.5} \times 38 = 34.8 \text{ g}$$

Hence, theoretical yield of *p*-acetamidobenzene sulphonamide = **34.8 g**

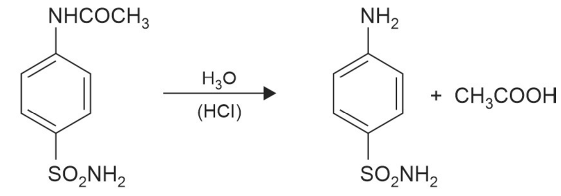
Sulphanilamide:

Reaction C: Add 15 g of the above thoroughly drained sulphonamide to 10 ml of concentrated hydrochloric acid diluted with 20 ml water, and boil the mixture gently under reflux for 1 hour. Then add 30 ml of water and heat the mixture again to boiling, with the addition of a small quantity of animal charcoal. Filter the boiling solution, and add powdered sodium carbonate in small quantities to the filtrate with stirring until all effervescence ceases and the sulphanilamide is precipitated as a white powder. Cool the mixture thoroughly and filter off the sulphanilamide at the pump, wash with water and dry.

Purify by recrystallisation from hot water: The sulphanilamide is obtained as colourless crystals, mp 163–165°C.

Theoretical Yield

Reaction C: The theoretical yield is usually calculated from the equation under theory:



p-Acetamidobenzene-sulphonamide

p-Acetamidobenzene-sulphonamide

214 g of *p*-acetamidobenzene sulphonamide on reacting with concentrated hydrochloric acid diluted with water yields sulphanilamide = 172 g

34.8 g of *p*-acetamidobenzene sulphonamide shall yield sulphanilamide

$$= \frac{172}{214} \times 34.8 = 27.9 \text{ g}$$

Hence, theoretical yield of sulphanilamide = **27.9 g**

Precautions

1. All glass apparatus to be used in the synthesis must be perfectly dried in an oven.
2. The chlorosulphonic acid should be handled *with great care,* and always in a fume cupboard. The technical acid is usually pure enough for the above preparation. If it is dark in colour, it can be further purified *by careful* distillation (preferably in an all-glass apparatus) and the fraction of bp 149–152° collected for use.

Characterization

Physical appearance: White crystalline compound
Melting point: 163–165°C
UV$_{max}$: 255, 312 nm
Odour: Odourless
TLC solvent: Chloroform-n-heptane-ethanol (3:3:3, v/v/v)

Uses

Sulphanilamide is the basic ring structure present in several sulpha drugs, which are examples of antibacterial in nature. Some examples of sulpha drugs are sulfadimidine, sulfaguanidine, sulfathiazole, sulphamethoxazole, etc. It is used in medicine in the treatment of bacterial infections.

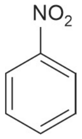
EXPERIMENT 32: TO PREPARE AND SUBMIT NITROBENZENE

Requirements

Nitric acid, sulphuric acid, benzene and sodium carbonate.

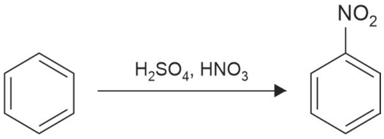
Theory

Chemical formula: $C_6H_5NO_2$
Molecular weight: 123.11
Boiling point: 211°C
Chemical name: Nitrobenzol and nitrobenzene



Nitrobenzene is prepared by heating benzene with a mixture of concentrated nitric acid and sulphuric acid at 50°C.

Chemical Reaction



Physical Properties

Colourless to pale yellow, oily liquid, odour of volatile oil almond poisonous use only with adequate ventilation BP 210–211°C. It is used as a solvent because of their high polarity, for the synthesis of amino compounds since they are easily available by direct nitration of arenes and other aromatic compounds. As explosives particularly trinitrobenzene and trinitro toluene.

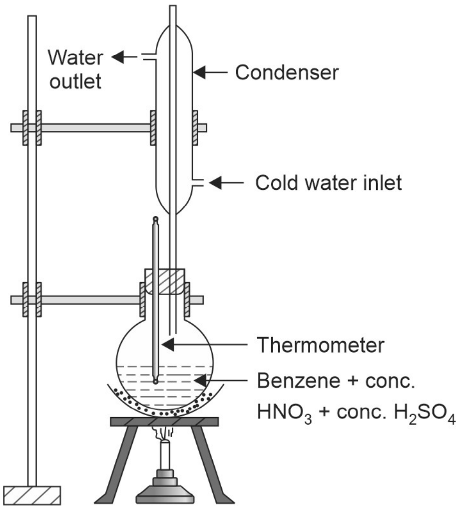


Fig. 2.1: Laboratory preparation of nitrobenzene (reflux)

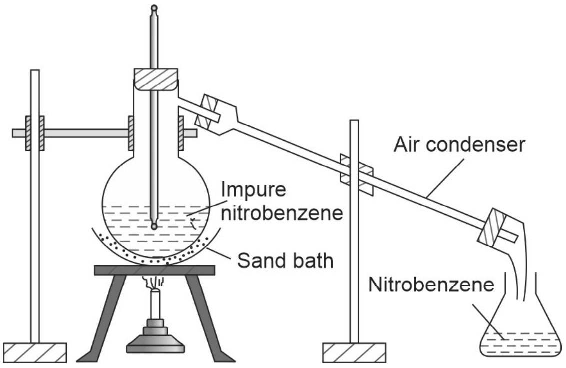


Fig. 2.2: Distillation of nitrobenzene (for purification)

Chemicals Required

Nitric acid	35 ml
Sulphuric acid	40 ml
Benzene	29 ml

Procedure

1. Place nitric acid 35 ml in 500 ml round bottom flask and add slowly 40 ml of conc. sulphuric acid and keeping mixture cold by water bath.
2. Add 29 ml of benzene in mixture of step 1 very slowly in fraction of 3 ml at a time. So that temperature should not rise to above 50°C till all benzene is added.

3. Fit a reflux water condenser to the flasks and keep it on water bath at temperature 60°C for 45 minutes with occasional shaking so as to mix nitrobenzene layer with acid layer below.
4. After 45 minutes pour contents of the flask into approx 300 ml cold water, in which nitrobenzene, which is heavier than, water sinks to the bottom.
5. Shake well to remove acid from nitrobenzene.
6. Decant off upper acid layer and transfer organic layer to separating funnel.
7. Shake with equal volume of water and allow separating.
8. Shake organic layer (nitrobenzene) with sodium carbonate solution till cessation of evolution of carbon dioxide.
9. Nitrobenzene is again washed with water to get it free from traces of sodium carbonate.
10. Transfer nitrobenzene to small flask, add some $CaCl_2$ till clear nitrobenzene (dried one).
11. Distill it at 207–211°C.

Result

Nitrobenzene is prepared and submitted.

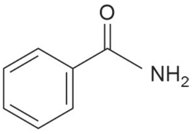
EXPERIMENT 33: TO PREPARE AND SUBMIT BENZAMIDE

Requirements

Benzoyl chloride, liquid NH_3 and distilled water.

Theory

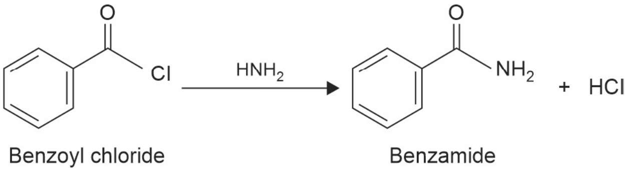
Chemical formula: C_7H_7NO, $C_6H_5CONH_2$
Molecular weight: 121.4
Melting point: 130°C
Chemical name: Benzoylamide



Benzamide

Benzamide is prepared from benzoyl chloride and ammonium carbonate. Alternate procedure using conc. ammonia solution. Benzoyl chloride is a colour less liquid, BP 197°C. It is insoluble in water has a pungent odour causes profuse watering of eyes. So, it is used in tear gas to disperse mobs and for introducing benzoyl group in hydroxy and amino compound. When reacted with liquor ammonia benzoyl chloride forms benzamide.

Chemical Reaction



Chemicals Required

Benzoyl chloride	12.1 g (10.00 ml)
Liquor NH_3 (aq)	50 ml

Procedure

1. Place 50 ml liq. NH_3 in 250 ml conical flask and cool in water bath fit a rod stirrer in it/magnetic stirrer to it and shake vigorously.
2. Add drop by drop 10 ml of benzoyl chloride in the conical flask of step 1.
3. Filter off the precipitated benzamide wash with cold water.
4. Recystallize with 50 ml of water to get pure benzamide.

Result

Benzamide is prepared and submitted.

EXPERIMENT 34: SYNTHESIS AND CHARACTERIZATION OF BENZIMIDAZOLE

Requirements

o-Phenylenediamine: 27 g, formic acid (90%): 16 ml, sodium hydroxide solution (10%).

Theory

o-Phenylenediamine condenses with formic acid to yield benzimidazole:

With acetic acid, 2-methylbenzimidazole, mp 173–174°C is formed: indeed the conversion of aliphatic acids into 2-alkylbenzimidazoles has been proposed as a method for preparing solid derivatives for the identification of monobasic aliphatic acids. Benzimidazole is an example of intermediate used in bulk drug industry. It is the nucleus present in drugs like mebendazole and thiabendazole.

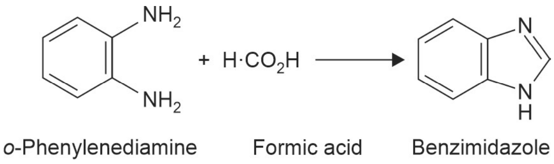
Procedure

1. Place 27 g of *o*-phenylenediamine in a 250 ml round bottomed flask and add 17.5 g (16 ml, 0.34 mol) of 90% formic acid.
2. Heat the mixture on a water bath at 100ºC for 2 hours. Cool, add 10% sodium hydroxide solution slowly, with constant rotation of the flask, until the mixture is just alkaline to litmus.
3. Filter off the crude benzimidazole at the pump, wash with ice-cold water, drain well and wash again with 25 ml of cold water.
4. Dissolve the crude product in 400 ml of boiling water, add 2 g of decolourising carbon and digest for 15 min. Filter rapidly at the pump through a Buchner funnel and flask. Cool the filtrate to about 10ºC, filter off the benzimidazole, wash with 25 ml of cold water and dry at 100ºC.

   The yield of pure benzimidazole, mp 171–172ºC, is 25 g (85%).

Theoretical Yield

The theoretical yield is usually calculated from the equation under theory:



1 mole of *o*-phenylenediamine reacts with 1 mole of formic acid to give 1 mole of benzimidazole.

As 1 mole of a substance is equal to the molecular mass of the substance,

108 g of *o*-phenylenediamine on reacting with 46 g of formic acid yields benzimidazole = 118 g

27 g of *o*-phenylenediamine shall yield benzimidazole

$$= \frac{118}{108} \times 27 = 29.5 \text{ g}$$

Hence, theoretical yield of aspirin = **29.5 g**

Characterization

Physical appearance: White to slightly beige powder

Melting point: 171–172°C

UV$_{max}$: Water at 245 nm

Odour: Weak amine like odour, characteristic

Solubility: Freely soluble in alcohol, sparingly soluble in ether.

TLC solvent: 7:3 mixture of ethyl acetate/hexane

EXPERIMENT 35: TO PREPARE AND SUBMIT ACETANILIDE FROM ANILINE (ACETYLATION)

Requirements

Aniline, acetic anhydride, glacial acetic acid and zinc dust.

Theory

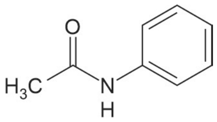
Chemical formula: C_8H_9NO

Molecular weight: 135.17

Melting point: 114 °C

Boiling point: 304 °C

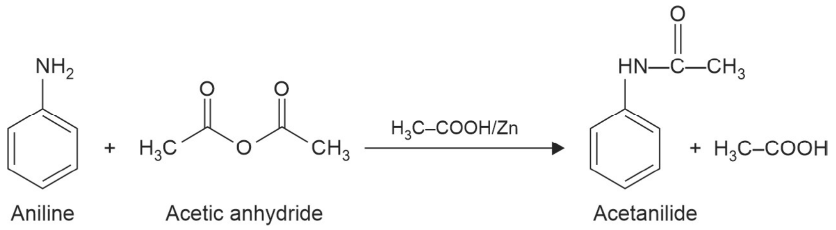
Chemical name: N-phenylacetamide, n-phenylethanamide



The principle involved in the preparation of acetanilide is acetylation. Acetylation is done by using a mixture of acetic anhydride and sodium acetate or acetic anhydride and acetic acid. When aniline is treated with acetic anhydride and sodium acetate, it gets acetylated to give acetanilide.

Acetanilide is prepared from aniline when it reacts with acetic anhydride/glacial acetic acid in the presence of zinc dust. A mixture of aniline, glacial acetic acid, acetic anhydride and zinc dust is refluxed under anhydrous condition and then poured the mixture into ice cold water to get acetic anhydride precipitate. The crude precipitate of acetic anhydride is recrystallized to get pure crystals of acetanilide.

Chemical Reaction



Properties

It is a white, odorless solid with a flaky appearance. Acetanilide is a little soluble in water. It is also soluble in diethyl ether, ethanol, benzene and acetone.

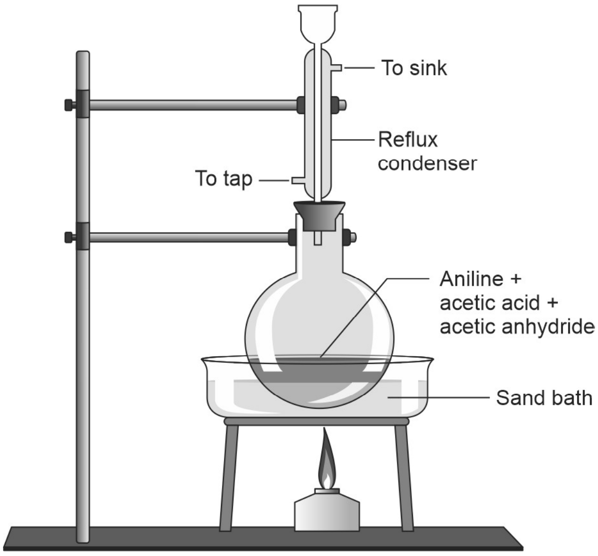


Fig. 2.3: Preparation of acetanilide

Chemicals Required

Aniline	20 ml
Acetic anhydride	20 ml
Glacial acetic acid	20 ml

Procedure

1. Take 20 ml of aniline, 20 ml acetic anhydride and 20 ml glacial acetic acid in 250 ml round bottom flask and add zinc dust.
2. Fix the reflux condenser with the round bottom flask.
3. Heat the mixture gently for about 15–20 minutes on sand bath.
4. Pour the hot mixture in a beaker containing ice cold water with constant stirring.
5. Stir the mixture vigorously to hydrolyze excess of acetic anhydride.
6. Once all the acetanilide is precipitate collect and filter in Büchner funnel.
7. The precipitate obtained as a crude sample of acetanilide.
8. To get the pure crystals by crystallization should be carried out.

9. For crystallization transfer the crude sample into a beaker containing 20 ml water and heat gently.
10. If the solution is colored then add small amount of activated carbon.
11. Filter the hot solution with funnel.
12. Cool the mixture for 30 minutes so that white spiny crystals of acetanilide separate out.
13. Filter off the crystal, wash them with water and dry in the folder of filter paper.

Uses

It is used as a precursor for synthesizing pharmaceuticals like penicillin, in the intermediation in accelerator synthesis of rubber, for stabilizing cellulose ester varnishes, for manufacturing of sulfa drugs.

Result

Acetanilide is prepared and submitted.

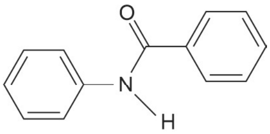
EXPERIMENT 36: TO PREPARE AND SUBMIT BENZANILIDE FROM ANILINE (SCHOTTEN-BAUMANN REACTION)

Requirements

Aniline, benzoyl chloride and 10% sodium hydroxide.

Theory

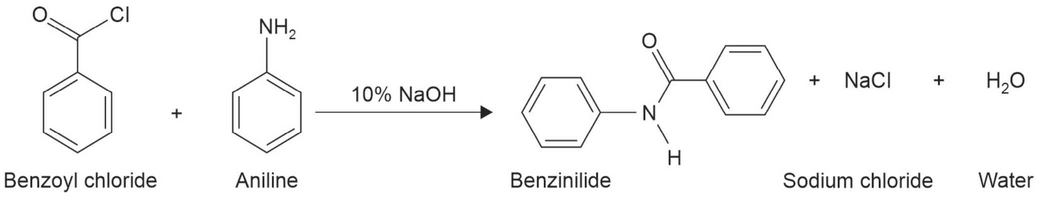
Chemical formula: $C_{13}H_{11}NO$
Molecular weight: 197
Melting point: 162–164 °C
Chemical name: N-Phenylbenzamide, n-benzoylaniline benzamide



Benzinilide

Benzanilide is an aromatic anilide. The principle involved in the preparation of benzanilide is benzoylation. When treated with benzoyl chloride in the presence of aqueous sodium hydroxide to give benzanilide. The aqueous sodium hydroxide is used to remove benzoyl chloride which gives sodium benzoate and hydrochloric acid. This reaction is called Schotten-Baumann method of benzoylation.

Chemical Reaction



Chemicals Required

Aniline	3 ml
Benzoyl chloride	5 ml
NaOH	4 ml
Alcohol	5 ml

Procedure

1. Place 3 ml aniline and 40 ml sodium hydroxide solution (10%) in 250 ml conical flask, mix well.
2. Add slowly 5 ml benzoyl chloride with vigorous shaking for 15–20 minutes until the smell of benzoyl chloride ceases completely.
3. Dilute the reaction mixture with 100 ml water.
4. Filter off the crude benzanilide with suction on a Büchner funnel.
5. Collect the precipitate and wash with cold water and recrystallize from alcohol.
6. Determine the melting point and practical yield of the final product.

Result

Benzanilide is prepared and submitted.

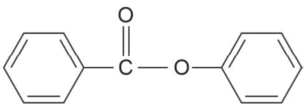
EXPERIMENT 37: TO PREPARE AND SUBMIT PHENYL BENZOATE FROM PHENOL (SCHOTTEN-BAUMANN REACTION)

Requirements

Phenol, benzoyal chloride, 10% NaOH and methanol.

Theory

Chemical formula: $C_{13}H_{10}O_2$
Molecular weight: 198
Melting point: 68–70ºC
Boiling point: 158ºC
Chemical name: Diphenylcarboxylate benzoic acid



Principle

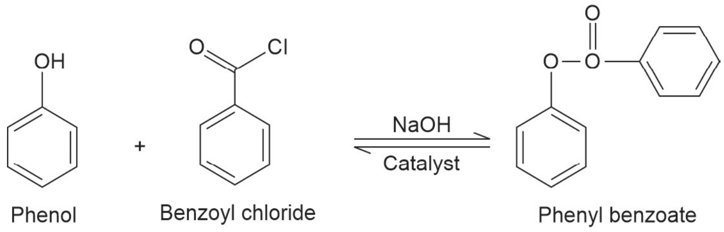
Synthesis of phenyl benzoate from phenol is an example of Schotten-Baumann reaction where phenols react with an aromatic acid chloride in the presence of an excess of a base at room temperature to form an ester. In this reaction, phenol is shaken with benzoyl chloride and excess amount of sodium hydroxide solution, it is benzoylated to give the ester, phenyl benzoate. The introduction of a benzoyl group in place of the active hydrogen of hydroxyl, amino group is known as benzoylation 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. Benzyl benzoate is an organic compound which is used as a medication and insect repellent. As a medication it is used to treat scabies and lice.

Chemicals Required

Phenol	1 g
Benzoyl chloride	2 ml
10% NaOH	15 ml
Methanol	100 ml

Phenyl benzoate is a phenyl ester of benzoic acid. Phenol is treated with benzoyl chloride in presence of sodium hydroxide for preparation phenyl benzoate.

Chemical Reaction



Procedure

1. Take a 1 g of phenol and add a 15 ml of 10% sodium hydroxide solution in a 250 ml conical flask and shake well at room temperature.
2. Carefully add 2 ml of benzoyl chloride (under fume cup hood). Stopper the flask and shake it vigorously for 15–20 minutes until odour of benzoyl chloride disappear.
3. Filter with suction pump on Buchner funnel and then wash thoroughly with ice water.
4. Recrystallize from methanol.
5. Weigh the recrystallized phenyl benzoate and calculate the practical yield.
6. Determine the melting point of the synthesized phenyl benzoate.

Calculation

Molecular weight of phenol (C_6H_6O) = 94 g/mol
Molecular weight of phenyl benzoate ($C_{13}H_{10}O_2$) = 198 g/mol

Theoretical Yield

94 g of phenol reacts with benzoyl chloride to gives a 198 g of phenyl benzoate.

Therefore, 1 g of phenol will give (X) g of phenyl benzoate.

$$X = (198 \times 1)/94 = 2.11 \text{ g}$$

Theoretical yield = 2.11 g

Practical yield = assume 1.8 g

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

$$\% \text{ yield } = \frac{1.8}{2.11} \times 100 = 85\%$$

Characterization

Physical appearance: Colourless crystals
Melting point: 69°C
Solubility: Water solubility 38.39 mg/L
TLC solvent: Toluene: Acetone (15:1)

Result

Phenyl benzoate is prepared and submitted.

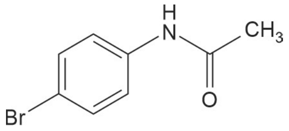
EXPERIMENT 38: TO PREPARE AND SUBMIT *p*-BROMO ACETANILIDE FROM ANILINE

Requirement

Acetanilide, bromine, sodium metabisulphite and glacial acetic acid.

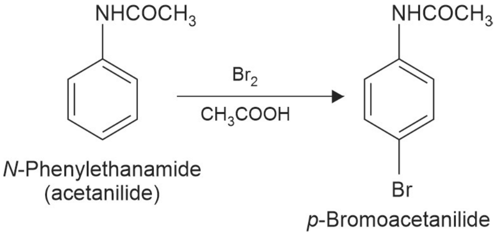
Theory

Molecular formula: C_8H_8BrNO
Molecular Weight: 214
Melting point: 168°C



The synthesis of *p*-bromo acetanilide is nuclear bromination. Bromination of acetanilide occurs at the para position due to the amine substituent, this substituent provides resonance stabilization to the carbocations created by para and ortho position. Bromination of acetanilide occurs at the para position, the function of the catalyst is to increase the electrophilic activity of halogen. It is sparingly soluble in hot water; benzene, chloroform, ethyl acetate; moderately soluble in alcohol. It is used as analgesic and antipyretic.

Chemical Reaction



Procedure

1. Powder 6 g acetanilide and dissolves in 22.5 ml of glacial acetic acid in 500 ml conical flask.
2. Dissolves 3 ml of bromine in 12.5 ml of glacial acetic acid and transfer the solution to separating funnel.
3. Add bromine solutions slowly and with constant shaking to ensure through mixing and stand the flask in cold water.
4. When bromine has been added to the solution, the solution color will have an orange.
5. Allow the final reaction mixture to stand at room temperature for about 30 minutes with continues shaking.
6. Pour the reaction product into 200 ml of water, rinse the flask with about 50 ml of water.
7. Stir the mixture well and add sufficient sodium metabisulphite solution to remove the orange color.
8. Filter the crystalline precipitate with the help of funnel and wash with cold water and press as dry.
9. Recrystallize from methanol.

Result

p-bromoacetanilide is prepared and submitted.

EXPERIMENT 39: SYNTHESIS AND CHARACTERIZATION OF BENZANILIDE

Requirements

Aniline: 1 ml, benzoyl chloride: 1.5 ml, sodium hydroxide (10%): 15 ml.

Theory

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. It is *used* as an anti-atherosclerotic agent and also in the manufacture of dyes.

Procedure

The following steps may be adopted in a sequential manner:

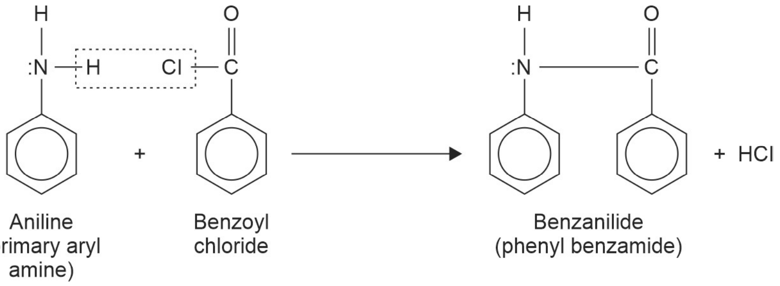
1. Add 1 ml of aniline to 15 ml of 10% aqueous sodium hydroxide solution contained in a wide-necked bottle as before, and then add 1.5 ml of benzoyl chloride, and shake vigorously for 15–20 minutes.
2. The mixture becomes warm and the crude benzoyl derivative separates as a white powder, or, if the shaking has not been sufficiently vigorous, as small pellets: When

the reaction is complete, filter off the product at the pump, break up any pellets with a spatula on the filter, and then thoroughly wash with water and drain.

3. Recrystallize the benzanilide from hot methylated spirit: For this purpose use rather more of the hot solvent than the minimum required for complete solution, and filter the latter through a funnel preheated by the filtration of some of the boiling solvent, as the benzanilide may crystallize rapidly as the solution cools: It is only slightly soluble in cold methylated spirit. Benzanilide is thus obtained as colourless crystals, mp 163°: yield, 1–6 g.

Theoretical Yield

The theoretical yield may be calculated from the equation:



93 g of aniline after reacting with benzoyl chloride yields benzanilide = 197 g

1.04 g of aniline shall yield benzanilide

$$= \frac{197}{93} \times 1.04 = 2.2 \text{ g}$$

Hence, theoretical yield of benzanilide = **2.2 g**

Characterization

Physical appearance: colourless crystals

Melting point: 163°C

Odour: Odourless

Solubility: Sparingly soluble in cold water

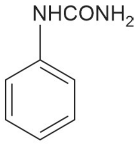
TLC solvent: DCM: Methanol (19:1)

EXPERIMENT 40: TO PREPARE AND SUBMIT PHENYL UREA

Requirements

Aniline hydrochloride, urea, concentrated hydrochloric acid, glacial acetic acid, ethyl acetate.

Theory

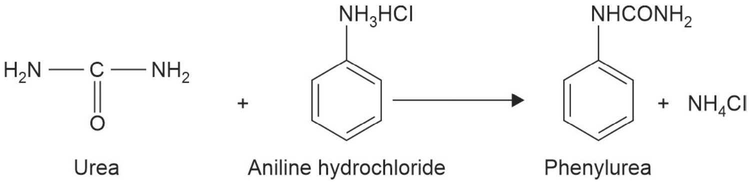


Phenylurea

Chemical formula: $C_7H_8N_2O$
Molecular weight: 136
Melting point: 145–147°C
Boiling point: 238°C
Chemical Name: 1-Phenylurea

It is a white to yellow crystal. Slightly soluble in water and completely soluble in other organic solvent such as acetone, ethanol, diethyl ether. Phenyl urea may be used as an herbicide for agriculture and agrochemicals preparation. Phenyl urea is benzoyl urea derivative substituted with phenyl group on the opposite nitrogen atom. Phenylurea can be prepared from aniline salts with urea in aqueous solution. Phenyl urea can be synthesized by the reaction of aniline hydrochloride with glacial acetic acid.

Chemical Reaction



Procedure

1. Dissolve 65 g (0.5 mol) of aniline hydrochloride and 120 g (2 mol) of urea in 200 ml of water contained in a 1-litre round-bottomed flask.
2. Filter the solution, if necessary.
3. Add 4 ml of concentrated hydrochloric acid and 4 ml of glacial acetic acid.
4. Fit a reflux condenser to the flask, introduce a few fragments of broken porcelain and boil the mixture for 30 minutes.
5. Fine white crystals appear after about 15 minutes and gradually increase in amount as the refluxing is continued.
6. Cool the flask in ice bath and filter with suction.
7. Separate the mixture of phenylurea and diphenylurea by boiling with 500 ml of water.
8. Filter at the pump through a preheated Buchner funnel into a warm flask (Phenylurea dissolved in boiling water while diphenylurea remain undissolved).
9. Cool the filtrate, collect the phenylurea, drain well and dry in the steam oven.
10. Recrystallisation from alcohol/glacial acetic acid/ethyl acetate with the addition of a little decolorizing carbon.

Calculation

Molecular weight of aniline hydrochloride ($C_6H_5N.HCl$) = 129.59 g/mol
Molecular weight of phenyl urea ($C_7H_8N_2O$) = 136.151 g/mol

Theoretical Yield

129.59 g of aniline hydrochloride reacts with acetic anhydride to gives a136.151 g of phenyl urea.

Therefore, 6.5 g of aniline hydrochloride will give (X) g of phenyl urea.

$$X = (136.151 \times 6.5)/129.59 = 6.82 \text{ g}$$

$$\text{Theoretical yield} = 6.82 \text{ g}$$

$$\text{Practical yield} = \text{Assume } 5 \text{ g}$$

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

$$\% \text{ yield} = \frac{5}{6.82} \times 100 = 73.31\%$$

Result

Phenyl urea is prepared and submitted.

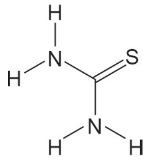
EXPERIMENT 41: TO PREPARE AND SUBMIT THIOUREA

Requirements

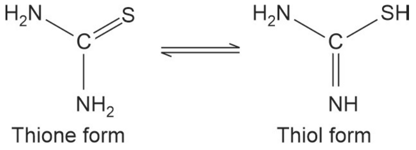
Ammonium thiocyanate, water.

Theory

Chemical formula: $SC(NH_2)_2$
Molecular weight: 76
Melting point: 182°C



Thiourea is an organosulfur compound with the formula $SC(NH_2)_2$. Thiourea is a reagent in organic synthesis. 'Thioureas' refer to a broad class of compounds with the general structure $(R^1R^2N)(R^3R^4N)C{=}S$. The material has the unusual property of changing to ammonium thiocyanate upon heating above 130°C. Upon cooling, the ammonium salt converts back to thiourea. Thiourea occurs in two tautomeric forms. In aqueous solution, the thione shown on the left below predominates:



Applications

Thiourea is used in textile processing, organic synthesis, silver polishing, and source of sulfide and as catalysts.

Physical Characterization

White solid moderately soluble in water.

Procedure

1. Place 50 g of ammonium thiocyanate in round bottom flask and immerse the thermometer.
2. Heat on an oil bath until the temperature rises to 170°C and maintain it at this temperature for 1 hr.
3. Allow the melt to cool and extract with 60–70 ml of hot water.
4. Filter the solution and allow cooling where the crude thiourea separates and the unchanged ammonium thiocyanate remains in the solution.
5. Filter the product and recrystallize the crude material with hot water to obtain thiourea as needle shape crystals.

Result

Thiourea is prepared and submitted.

EXPERIMENT 42: TO PREPARE AND SUBMIT IODOFORM FROM ETHANOL (HALOFORM REACTION)

Requirements

Ethyl alcohol, iodine, sodium carbonate and sodium hydroxide.

Chemical Reaction

$$\underset{\text{Ethyl alcohol}}{C_2H_5OH} + 4I_2 + 3Na_2CO_3 \rightarrow \underset{\text{Iodoform}}{CHI} + 5NaI + HCOONa + CO_2 + 2H_2O$$

Theory

Chemical formula: CHI_3
Molecular weight: 393.73
Melting point: 121°C
Chemical name: Carbon triiodide

Iodoform is a yellow colored crystalline solid with melting point 121°C. It has a characteristic unpleasant odor. It is insoluble in water but readily dissolves in ethyl alcohol and ether. Due to liberation of free iodine it has an antiseptic action. On heating, iodoform decomposes to give iodine vapor. This reaction is accelerated by moisture, air or light. Iodoform is used as a rubifacient. It is a topical analgesic creating heat on applied area. It also acts as antiseptic because of presence of iodine in its structure.

Chemicals Required

Ethanol	20 ml
Iodine	3 g
Sodium carbonate	40 g

Procedure

1. Take ethyl alcohol (20 ml), sodium carbonate (40 g) and water (20 ml) in 500 ml round bottomed flask.
2. Heat the flask to about 70–80°C on a water bath to warm the solution.

3. Add small amount of iodine at a time with constant shaking add more iodine so that the reaction product should have a pale yellow colour.
4. Add dropwise a dilute solution of sodium hydroxide if any brown colour of iodine persists.
5. Filter the crude iodoform, wash with cold water and recrystallize from hot ethanol to obtain the yellow crystals.

Result

Iodoform is prepared and submitted.

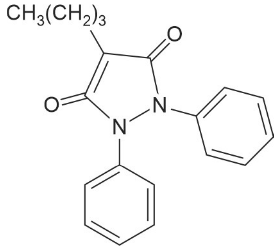
EXPERIMENT 43: TO PREPARE AND SUBMIT PHENYLBUTAZONE

Requirements

Diethylether, diethyl-n-butyl malonate/n-butyl malonyl chloride, $NaHCO_3$, diphenylhydrazine, HCl, ether, pyridine.

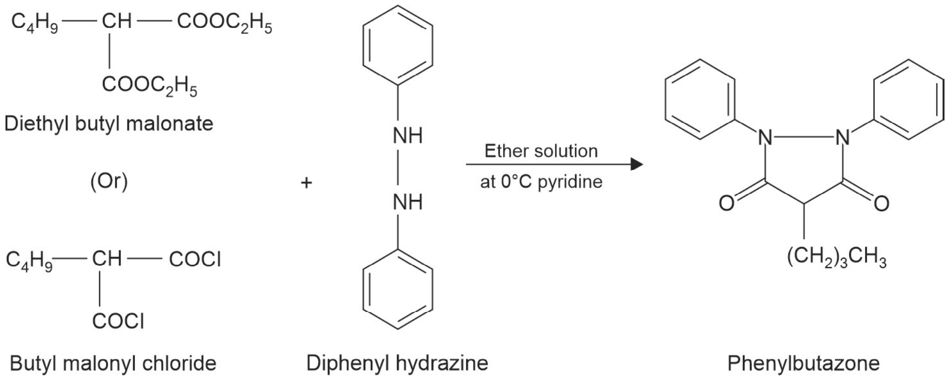
Theory

Chemical formula: $C_{19}H_{20}N_2O_2$/$C_{19}H_{19}N_2NaO_2$ (sodium salt)
Molecular weight: 308
Melting point: 164–166°C
Chemical name: 4-butyl-1,2-diphenyl-3,5-pyrazolidinedione



Phenylbutazone is used as a non-steroidal anti-inflammatory drug (NSAID) for the treatment of chronic pain, including the symptoms of rheumatoid arthritis, and osteoarthritis. Its use is limited by such severe side effects as suppression of white blood cell production, aplastic anemia and granulomas. Phenylbutazone is synthesized in a single stage by reacting hydrazobenzol with butylmalonic ester.

Chemical Reaction



Procedure

1. In a 250 ml round bottom flask take diethyl-*n*-butyl malonate or *n*-butyl malonyl chloride (1 mole) and hydrazobenzene (diphenylhydrazine 1 mole) in 25 ml of diethylether.
2. Cool the solution to 0°C and add pyridine (1 mole).
3. Follow the reaction on TLC and once complete transfer the contents to 250 ml separating funnel.
4. Extract with aq. HCl (2 × 10 ml), followed by extraction with aq. sodium bicarbonate (3 × 25 ml).
5. Combine the aq. sodium bicarbonate fractions and precipitate the phenylbutazone with slow addition of hydrochloric acid.
6. Filter the crystals of phenylbutazone and recrystallize with suitable solvent.

Result

Phenylbutazone is prepared and submitted.

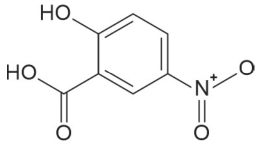
EXPERIMENT 44: TO PREPARE AND SUBMIT 5-NITRO SALICYLIC ACID

Requirements

Chemical—calcium nitrate, acetic acid and salicylic acid

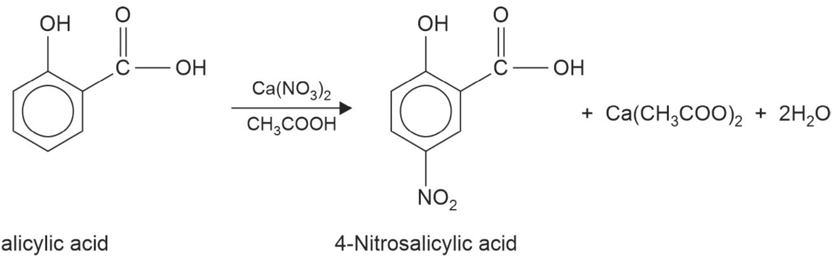
Theory

Chemical formula: $C_7H_5NO_5$
Molecular weight: 183
Melting point: 399°C



Nitration on salicylic acid occurs by placing a nitro group on the aromatic ring system via an electrophilic aromatic substitution reaction. Two group COOH and –OH in salicylic acid complement each other since they both direct the entering nitro group to the 5th position. The 5th position and 3rd position are both electronically favored, the –COOH group is meta directing and the –OH group is ortho, para directing. The nitro group is attached at the 5th position and not at the 3rd position due to the steric effect.

Chemical Reaction



Salicylic acid 4-Nitrosalicylic acid

Procedure

1. Dissolve 6 g of calcium nitrate in 20 ml of acetic acid within 250 ml conical flask and gently heat on a water bath.
2. To the above mixture add 4 g of salicylic acid and heat (below 80°C) on a boiling water bath for few minutes, dark red solution is formed.
3. Then the reaction mixture is pour into 250 ml beaker containing 20 ml ice cold water.
4. The solution is keep refrigerator and after 4–5 hr yellow crystals of 5-nitrosalicylic acid is separates out.
5. The crude product is filtered at the suction pump, washed with cold water and dried.

Calculation

138 g of salicylic acid gives 198 g of 5-nitrosalicylic acid.
Therefore, 2 g of salicylic acis will give (X) g of 5-nitrosalicylic acid.

$$x = \frac{198 \times 2}{138} = 2.87 \text{ g}$$

If practical yield is 1.32 g, then

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

$$= \frac{1.32}{2.87} \times 100 = 46\%$$

Result

5-nitro salicylic acid is prepared and submitted.

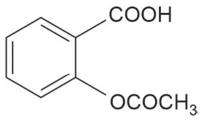
EXPERIMENT 45: TO PREPARE AND SUBMIT ASPIRIN

Requirements

Salicylic acid, acetylchloride, pyridine.

Theory

Chemical formula: $C_9H_8O_4$
Molecular weight: 180
Melting point: 135 °C
Chemical name: Acetylsalicylic acid

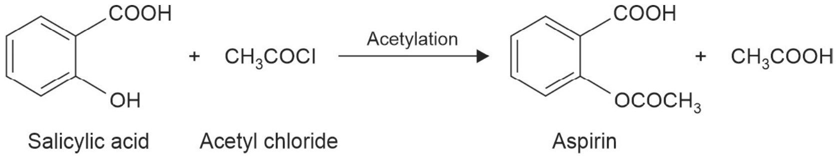


Aspirin

Aspirin is also known as acetyl salicylic acid. It is a widely used drug in modern society. It is an analgesic (pain killer), a powerful antipyretic (fever-reducing) and an anti-inflammatory (swelling-reducing) substance. Salicylic acid is itself an analgesic and was originally administered as sodium salicylate. Since salicylic acid has an irritating effect on the stomach lining. Conversion to the ester satisfied this requirement and acetylsalicylic acid (*aspirin*) proved to be as effective as sodium salicylate without the irritation typical of phenolic compounds. Aspirin gets, however, hydrolyzed to salicylic acid in the alkaline medium of the intestines.

The principle involved in synthesis of aspirin acetylation where the hydroxylic group present in salicylic acid is acetylated by using acetyl chloride or acetic anhydride. Aspirin is obtained from salicylic acid by simple acetylation with acetic anhydride or acetyl chloride in the presence of sulfuric acid as catalyst. Because of its low solubility in water it is isolated from the reaction mixture by precipitation with water.

Chemical Reaction



Chemicals Required

1. Salicylic acid	10 g
2. Pyridine	7 ml
3. Acetyl chloride	7.5 ml

Procedure

1. Clean the glassware with chromic acid, wash and dry with acetone/methanol in oven.
2. Dissolve 10 g of salicylic acid in 7 ml of dry pyridine in 100 ml conical flasks warm to dissolve.
3. Add slowly 7.5 ml acetyl chloride with vigorous shaking of the flask of salicylic acid + pyridine at temperatyre 50–60°C cooling the flask occasionally in cold water, if necessary.
4. Heat at water bath for 5 minutes—cool to room temperature.
5. Pour in a thin stream into 300 ml cold water with vigorous shaking.
6. Acetylsalicylic acid crude solidifies as fine needles.
7. Filter wash with water and recystallize from equal volumes of water and acetic acid.
8. Acetylsalicylic acid is colorless crystal MP 135°C.

Result

Aspirin is prepared and submitted.

EXPERIMENT 46: SYNTHESIS AND CHARACTERIZATION OF ASPIRIN FROM SALICYLIC ACID

Requirements

Salicylic acid: 6 g, acetic anhydride: 10 ml, glacial acetic acid: 10 ml

Theory

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. The type of reaction is **acetylation.** Aspirin is used for the relief of minor aches and mild to moderate pain. It is recommended for arthritis and related arthritic conditions. It is also indicated for myocardial infarction prophylaxis. It is employed to reduce the risk of transient ischemic attacks in men.

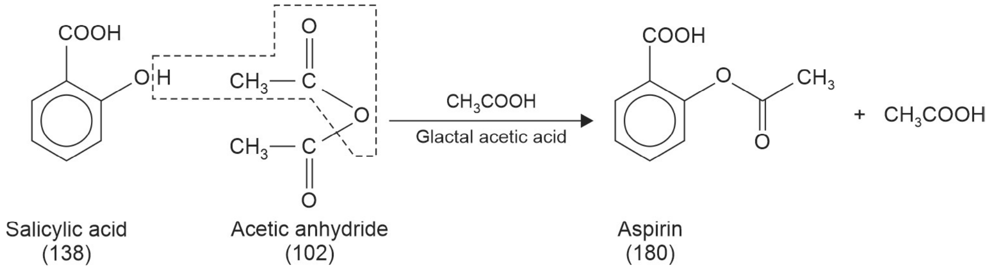
Procedure

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 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 Buchner 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.

Theoretical Yield

The theoretical yield is usually calculated from the equation under theory:



1 mole of salicylic acid reacts with 1 mole of acetic anhydride to give 1 mole of aspirin.

As 1 mole of a substance is equal to the molecular mass of the substance, 138 g of salicylic acid on reacting with 102 g of acetic anhydride yields aspirin = 180 g

∴ 6 g of salicylic acid shall yield aspirin

$$= \frac{180}{138} \times 6 = 7.82 \text{ g}$$

Hence, theoretical yield of aspirin = **7.82 g**

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.

Characterization

Physical appearance: Monoclinic tablets or needlelike crystals
Melting point: 135°C (rapid heating); the melt gets solidified at 118°C
UV$_{max}$ (0.1 NH_2SO_4): 229 nm [E (1% 1 cm) at 484 nm]; $CHCl_3$: 277 nm [E (1% 1 cm) at 68 nm]
Odour: 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
Solubility: 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.
TLC solvent: 50:50 mixture of ethyl acetate/hexane

EXPERIMENT 47: SYNTHESIS AND CHARACTERIZATION OF PARACETAMOL (ACETAMINOPHEN) FROM *p*-AMINOPHENOL (ACETYLATION)

Requirements

Nitrobenzene: 13 g (10.77 ml), dilute H_2SO_4: 25 ml, calcium carbonate: qs, benzene: 100 ml, activated carbon: 10 g, sodium hydrosulphite: 0.1 g, anhydrous sodium acetate: 7.5 g, acetic anhydride: 13.5 g.

Theory

Chemical formula: $C_8H_9NO_2$
Molecular weight: 155
Melting point: 169°C
Chemical name: N-(4-hydroxyphenyl) acetamide

Nitrobenzene on being subjected to electrolytic reduction in the presence of sulphuric acid yields *p*-aminophenol which on treatment with acetic anhydride and sodium acetate gives rise to the production of acetaminophen (or paracetamol).

Procedure

The various steps are adopted as follows:

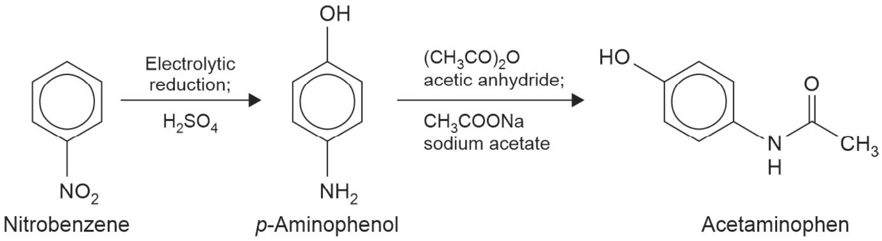
1. A reaction mixture consisting of 10.77 ml nitrobenzene 100 ml water plus 25 ml of dilute H_2SO_4 is subjected to *electrolytic reduction*; which yielded 11.5 g of *p*-aminophenol
2. The resulting reaction mixture containing *p*-aminophenol 11.5 g is neutralized, while at a temperature ranging between 60° and 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).
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 and 10°C, stirred and maintained at this particular temperature for 60 minutes.
8. A crystalline pure product, paracetamol, 13.5 g having mp 169–170.5°C, is obtained.

Theoretical Yield

The theoretical yield may be calculated from the equation:



123.11 g of nitrobenzene after conversion to *o*-aminophenol yields acetaminophen = 151.17 g

13 g of nitrobenzene shall yield acetaminophen

$$= \frac{151.17}{123.11} \times 13 = 15.96 \text{ g}$$

Hence, theoretical yield of acetaminophen = **15.96 g**

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.

Recrystallization

The product may be recrystallized by dissolving in minimum quantity of hot water when beautiful large monoclinic prisms obtained, 13 g, having mp 169.5–170.5°C.

Characterization

Physical appearance: Large monoclinic prisms from water

Melting point: 169–170.5°C

UV$_{\textbf{max}}$ (ethanol): 250 nm (∈ 13800)

Solubility

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.

Taste: Slightly bitter taste

pH (saturated solution): 5.3 to 6.5

TLC solvent: Chloroform-butanol (3:1)

Uses

It is invariably used as an effective antipyretic and analgesic. It is also effective in the treatment of a wide variety of arthritic and rheumatic conditions involving musculo-skeletal pain as well as the pain due to headache, dysmenorrhea, myalgias and neuralgias. It is also found to be useful in diseases accompanied by pain, discomfort, and fever, for instance: The common cold and other viral infections.

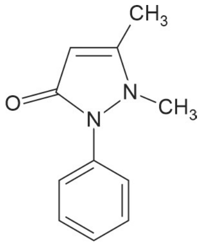
EXPERIMENT 48: SYNTHESIS AND CHARACTERIZATION OF ANTIPYRINE

Requirements

Phenylhydrazine, ethylacetoacetate, dimethylsulphate, Pet. ether, ethanol, sodium hydroxide, decolourising carbon.

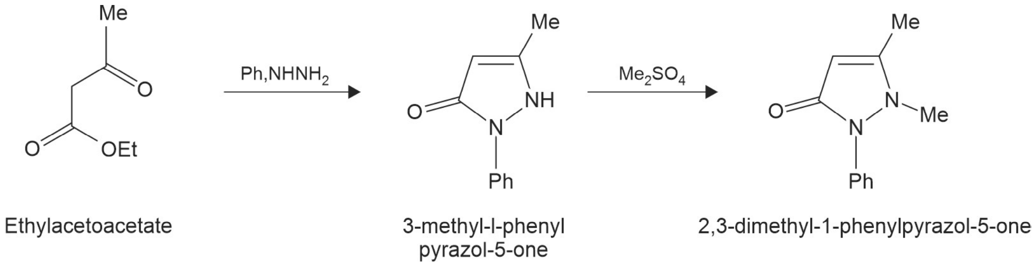
Theory

Chemical formula: $C_{11}H_{12}N_2O$
Molecular weight: 188
Melting point: 109–111°C
Chemical name: 2,3-Dimethyl-1-phenyl-3-pyrazolin-5-one



The basic nitrogen atom attached to the phenyl ring in the phenylhydrazine reacts with ethylacetoacetate to undergoes cyclization by the removal of ethanol and water molecule. Later the hydrogen attached to the adjacent nitrogen undergoes methylation in presence of dimethylsulphate to yield antipyrine. The preparation of methyl-phenyl-pyrazolone illustrates one of the synthetic uses of ethyl acetoacetate, as distinct from those involving the **hydrolysis** of substitution derivatives. If ethyl acetoacetate is warmed with an equivalent quantity of phenyl hydrazine, the corresponding phenyl hydrazone is readily formed. On further heating, **ring formation** occurs with the loss of ethanol and the production of methyl-phenyl-pyrazolone. It is used as anti-pyretic and analgesic.

Chemical Reaction



Procedure

Mix together 50 g (49 ml) of redistilled ethylacetoacetate and 40 g (36.5 ml) of phenylhydrazine in a large evaporating dish. Heat the mixture on a boiling water bath in the fume cupboard for about 2 hours and stir from time to time with a glassrod. Allow the heavy reddish syrup to cool somewhat, add about 100 ml of ether and stir the mixture vigorously. The syrup, which is insoluble in ether, will solidify within 15 minutes. Filter the solid at the pump and wash it thoroughly with ether to remove coloured impurities. Recrystallise it from hot water or from a mixture of equal volumes of ethanol and water.

Dissolve the product in 20 ml methanol. Add solution of 10 g sodium hydroxide in water dropwise in a fume cupboard. Warm the mixture on a waterbath. Add 36 g (27 ml) of dimethyl sulphate. Reflux for 1 hour. Cool with continuous stirring. Distill off methanol. Add hot water to residue, filter and extract antipyrine with benzene and evaporate the solvent.

Theoretical Yield

The theoretical yield may be calculated from the equation:

130 g of ethyl acetoacetate after reacting with phenyl hydrazine yields antipyrine = 162 g

∴ 6.4 g of ethyl acetoacetate shall yield antipyrine = 162/130 × 6.4 = 7.97 g

Hence, theoretical yield of antipyrine = $\frac{162}{130} \times 6.4$ = **7.97 g**

Characterization

Physical appearance: Colourless white crystals

Melting point: 127°C

UV$_{\text{max}}$ (ethanol): 254 nm

TLC Solvent: Chloroform: methanol (9:1)

Uses

It is used as an antipyretic and analgesic that has been given by mouth and as ear drops.

Result

Antipyrine is prepared and submitted.

EXPERIMENT 49: TO PREPARE AND SUBMIT SULPHANILAMIDE FROM ACETANILIDE

Requirements

Acetanilide, chlorosulphonic acid, ammonia, ethanol and hydrochloric acid.

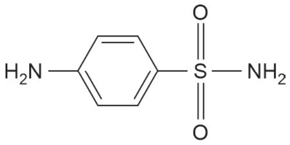
Theory

Chemical formula: $C_6H_8N_2O_2S$

Molecular weight: 172

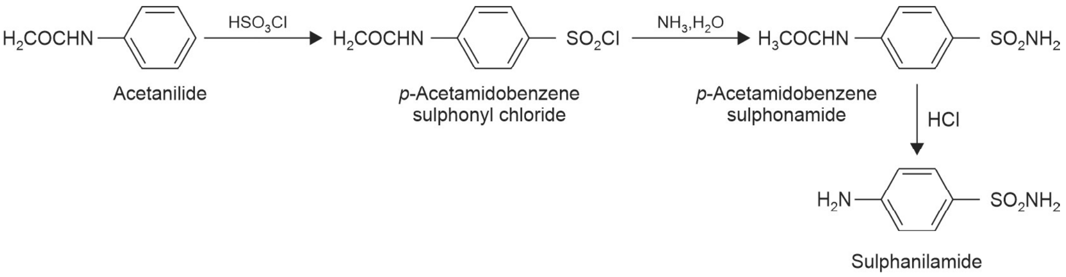
Melting point: 165.5 °C

Chemical name: Aminobenzene sulphonamide



Acetanilide undergoes chlorosulfonation by reacting with chlorosulfonic acid and there by obtained sulphonyl chloride reacts with ammonia solution to yield sulphonamide where the acetoxy group attached to the para position of sulphonamide gets detaches as acetylchloride by reacting with hydrochloric acid to offer sulphanilamide.

Chemical Reaction



Procedure

p-Acetamidobenzene Sulphonyl Chloride

Equip a 500 ml two-necked flask with a dropping funnel and a reflux condenser attach the top of the latter to a device for the absorption of hydrogen chloride. Place 20 g of dry acetanilide in the flask and 50 ml of a good grade of chlorosulphonic acid in the dropping funnel and insert a calcium chloride guard-tube into the latter. Add the chlorosulphonic acid in small portions and shake the flask from time to time to ensure thorough mixing. When the addition has been made, heat the reaction mixture on a water bath for1 hour in order to complete the reaction. Allow to cool and pour the oily mixture in a thin stream with stirring into 30 g of crushed ice (or ice-water) contained in a 1-litre beaker. Carryout this operation carefully in the fume cupboard since the excess of chlorosulphonic acid reacts vigorously with the water. Rinse the flask with a little ice-water and add therinsings to the contents of the beaker. Filter off the *p*-acetamido benzene sulphonyl chloride at the pump and wash it with a little cold water; press and drain well. Use the crude product immediately in the next stage.

p-Acetamidobenzene sulphonamide

Transfer the crude *p*-acetamidobenzene sulphonyl chloride to the rinsed reaction flask, and add a mixture of 70 ml of concentrated ammonia solution and 70 ml of water. Mix the contents of the flask thoroughly, and heat the mixture with occasional swirling (fume cupboard) to just below the boiling point for about 15 minutes. The sulphonyl chloride will be converted into a pasty suspension of the corresponding sulphonamide. Cool the suspension in ice, and then add dilute sulphuric acid until the mixture is just acid to Congo red paper. Collect the product on a Buchner funnel, wash with a little cold water and drain as completely as possible. It is desirable, but not essential, to dry the crude *p*-acetamidobenzene sulphonamide at 100°C.

p-Aminobenzene sulphonamide

Transfer the crude *p*-acetamidobenzene sulphonamide to a 500 ml flask; add 10 ml of concentrated hydrochloric acid and 30 ml of water. Boil the mixture gently under reflux for 30–45 minutes. The solution, when cooled to room temperature, should deposit no solid amide; if a solid separates heat for a further short period. Treat the cooled solution with 2 g of decolourising carbon, heat the mixture to boiling and filter with suction through a hardened filter paper. Place the filtrate (a solution of sulphanilamide hydrochloride) in a litre beaker and cautiously add 16 g of solid sodium hydrogen carbonate in portions with stirring. After the evolution of gas has subsided, test the suspension with litmus paper and if it is still acid, add more sodium hydrogen carbonate until neutral. Cool in ice, filter off the sulphanilamide with suction and dry.

Category

Antibiotic.

Result

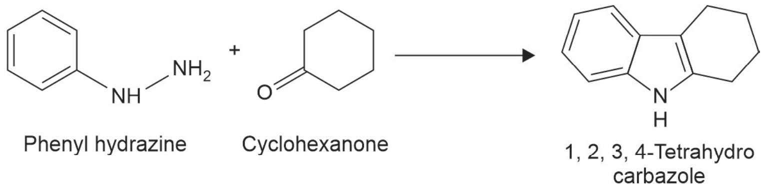
Sulphanilamide is prepared and submitted.

EXPERIMENT 50: TO PREPARE AND SUBMIT 1,2,3,4-TETRAHYDROCARBAZOLE (FISCHER INDOLE SYNTHESIS)

Theory

Tetrahydrocarbazoles can be prepared by heating cyclohexanone and phenyl hydrazines in presence of acid catalyst is known as Fischer indole synthesis. This ring system is also a part of several drugs.

Chemical Reaction



Procedure

Place cyclohexanone (4.75 g/5 ml) and glacial acetic acid (30 ml) in a round bottom flask and add phenylhydrazine (5.4 g/4.5 ml). Heat the mixture under reflux for 1 hour and then cool. Filter the brown precipitate using water pump. Wash the solid compound from cold water (4 × 50 ml). Leave the precipitate to dry at room temperature. Crystallize the product from aqueous alcohol.

Result

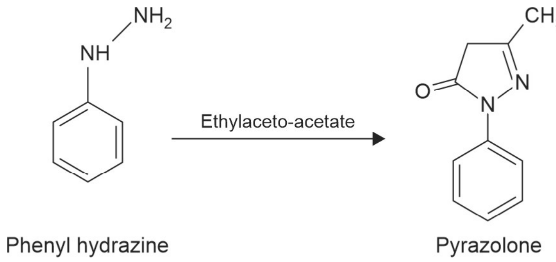
1,2,3,4-Tetrahydrocarbazole is prepared and submitted.

EXPERIMENT 51: TO PREPARE AND SUBMIT 3-METHYL-1-PHENYL-5-PYRAZOLONE.

Theory

Condensation of ethyl acetoacetate with phenylhydrazine produces phenylhydrazone derivative which cyclised to pyrazolone derivative. The pyrazole containing compounds show prominent biological actions. They are also used to prepare several pyrazolone-based drugs.

Chemical Reaction



Procedure

Place in 100 ml round bottom flask, freshly distilled phenyl hydrazine (5.4 g; 6.35 ml) and ethyl acetoacetate (6.4 g; 4.9 ml). Heat the mixture under reflux at 120°C for 1 hour. Cooling the red oily solution and add the ether (50 ml) with stirring to solidification the product. Filter the precipitate. Recrystallize the product from aqueous ethanol (50%).

Result

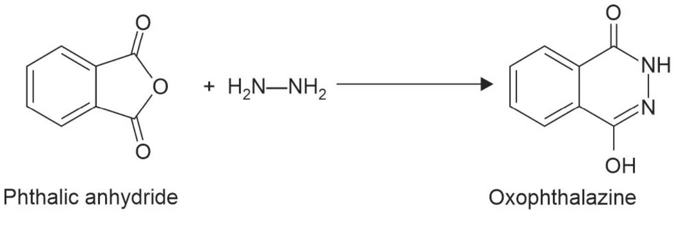
3-Methyl-1-phenyl-5-pyrazolone is prepared and submitted.

EXPERIMENT 52: TO PREPARE AND SUBMIT 3,4-DIHYDRO-1-HYDROXY-4-OXOPHTHALAZINE

Theory

The most famous coumarin is warfarin which is used in low doses in humans as a blood thinner. Coumarin can be prepared by the reaction of resorcinol with β-keto ester as ethyl acetoacetate in presence of acid condensation agents (Pechmann reaction).

Chemical Reaction



Procedure

Place in 100 ml round bottom flask, hydrazine hydrate (5.5 g) and phthalic anhydride (3 g) in ethanol (25 ml). Heat the mixture on water bath at 100ºC for half hour. Cool and filter the solution and then wash by petroleum ether (3 × 40 ml). Reduce the volume of solvent and keep at room temperature, a solid separates.

Result

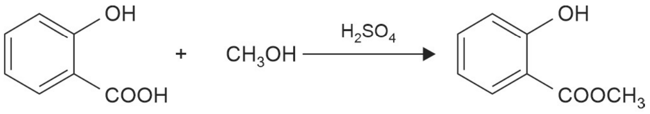
3,4-Dihydro-1-hydroxy-4-oxophthalazine is prepared and submitted.

EXPERIMENT 53: TO PREPARE AND SUBMIT METHYL SALICYLATE (OIL OF WINTERGREEN)

Theory

Methyl salicylate is also known as oil of wintergreen. It is prepared by the combination of methyl alcohol and salicylic acid in the presence of H_2SO_4. This process is known as esterification. In contrast to other salicylate, it is not used internally as it can induce vomiting, gastritis and systemic toxicity.

Chemical Reaction



Salicylic acid Methanol Methyl salicylate

Procedure

A solution of salicylic acid (17 g) absolute methyl alcohol (30 ml) and conc. H_2SO_4 (5 ml) is refluxed for 3 hr under anhydrous condition. Excess ethanol is removed by distillation (steam bath) and the residual product is poured into water. Methyl salicylate is extracted with ether. The ether extract is washed with Na_2CO_3 solution (till free of acid) and finally with water. It is dried and distilled. Characteristic smell of methyl salicylate (oil of Wintergreen) is obtained from the product.

Result

Methyl salicylate (oil of wintergreen) is prepared and submitted.

EXPERIMENT 54: TO PREPARE AND SUBMIT OXALIC ACID FROM SUCROSE

Theory

Oxalic acid is formed by the reaction between sucrose (cane sugar) and conc. HNO_3. It is a colourless compound and poisonous in nature. Its melting point is 101ºC.

Chemical Reaction

$$\underset{\text{Sucrose}}{C_{12}H_{22}O_{11}} + \underset{\substack{\text{From nitric}\\ \text{acid}}}{18[O]} \longrightarrow \underset{\text{Oxalic acid}}{6\,(COOH)_2} + 5H_2O$$

Procedure

Take 10 g cane sugar in a round bottom flask then add 50 ml HNO_3, then heat on the water bath. After 15 min, pour the reaction mixture into a conical flask. Allow the mixture to evaporate and reduce its volume to 10 ml. Now add 20 ml ice cold water into the conical flask. When crystals are formed, filter and recrystallize.

Result

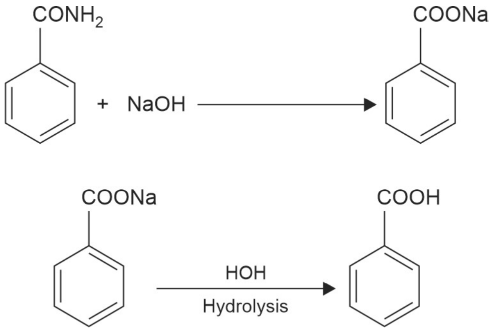
Oxalic acid is prepared and submitted.

EXPERIMENT 55: TO PREPARE AND SUBMIT BENZOIC ACID

Theory

Benzoic acid is simplest aromatic carboxylic acid. It is used for the preparation of various important compounds. Itself it acts as keratolytic and antifungal agent.

Chemical Reaction



Procedure

Placed the mixture of conc. NH_3 (10 ml) and water (5 ml) in a conical flask and shake vigorously and add benzoyl chloride drop by drop formed the benzamide as separated.

Take 1 g of formed benzamide and 10% NaOH (15 ml) in a RBF flask fitted with refluxes condenses and boil the mixture gently 30 min. ammonia is evolved then add con. H_2SO_4 after cooling the mixture until it becomes acidic ad benzoic acid is immediately separated out.

Result

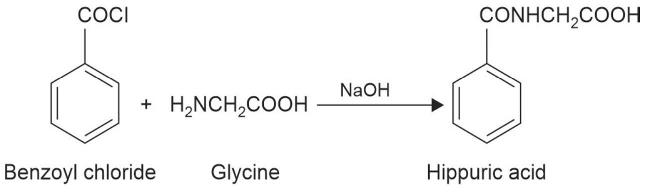
Benzoic acid is prepared and submitted.

EXPERIMENT 56: TO PREPARE AND SUBMIT HIPPURIC ACID

Theory

Hippuric acid is benzoyl glycine. It is synthesized from the amino acid glycine. Several compounds are synthesized from hippuric acid. It was isolated from horse urine, thats why its name is hippuric acid.

Chemical Reaction



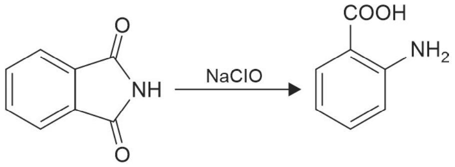
Procedure

Glycine (10 g) is dissolved in 100 ml of 10% NaOH in a conical flask. Then 18 ml of benzoyl chloride is added until all chloride has reacted. The reaction mixture is transferred into a beaker and the conical flask is rinsed with little water. Ice of few grams is placed into the reaction mixture. 1–2 ml of HCl is added and stirred vigorously until reaction mixture gets fully reacted with it. A precipitate is obtained which is filtered, washed thoroughly with water and finally with carbon tetrachloride. It is dried in dry air oven and recrystallized.

Result

Hippuric acid is prepared and submitted.

EXPERIMENT 57: TO PREPARE AND SUBMIT ANTHRANILIC ACID FROM PTHALIMIDE BY HOFMANN'S REARRANGEMENT REACTION



Procedure

Prepare a solution of 30 g of NaOH in 120 ml of water in 250 ml conical flask and cool to 0°C or below in a bath of ice. Add 26.2 g of bromine in one portion and shake until all bromine has reacted. Temperature will rise slightly again. Cool the mixture. Prepare solution of 22 g of NaOH in 80 ml of water. Add 24 g of phthalimide in a portion to cold NaOBr solution in terms of smooth paste with water rapidly with stirring. Remove the flask from cooling bath and shake vigorously until a clear yellow solution is obtained. Add prepared NaOH solution rapidly in one portion. Heat the solution at 80°C for about 2 minutes and filter if necessary. Cool in ice and add conc. HCl slowly with stirring until the solution is just neutral. Precipitate anthranilic acid completely by gradual addition of glacial acetic acid (20–25 ml will be required). Filter off the acid at pump and wash with a little cold water. Recrystallized from hot water with addition of little decolorizing agent. Collect the acid on Buckner funnel and dry at 100°C.