CHAPTER

# LOCAL ANTI-INFECTIVE AGENTS

1

## 1. INTRODUCTION

Invasion of the body by pathogenic microorganisms and the reaction of the host is known as infection. Anti-infective agents are drugs, which can either kill infectious agent or inhibit it from spreading. It includes antibiotics, antibacterial, antifungals, antivirals, antiprotozoans, disinfectant and antiseptic. The disinfectant and antiseptics are in general called anti-infective agents may be discussed under the following section.

Disinfection is the term, used for destruction of all pathogenic organisms such as vegetative forms of bacteria, mycobacterium, fungi and viruses but not spores. A chemical substance which causes disinfection is called disinfectant. It may be bactericidal or bacteriostatic. They are generally used to disinfect inanimate objects.

Antiseptic is an agent, which prevents sepsis by destroying or inhibiting the growth of microorganisms in the living tissues. It is applied before every invasive procedure, whether it is simple hypodermic infection or major surgery. These agents are applied topically without being absorbed systemically.

## 2. CLASSIFICATION

i) Alcohol and related compounds: e.g. Ethyl alcohol, Isopropyl alcohol, Ethylene oxide.

ii) Aldehydes: e.g. Formaldehyde solution, Glutaraldehyde.

iii) Phenols and its derivatives: e.g. Phenol, Liquified phenol, p-Chlorophenol, p-Chloro-m-xylenol, Hexachlorophene, Cresol, Chlorocresol, Thymol, Eugenol, Resorcinol, Hexylresorcinol.

iv) Oxidizing agents: e.g. Carbamide peroxide, Hydrous benzoyl peroxide.

v) Halogen containing compounds.

a) Iodine compound: e.g. Povidone-Iodine.

b) Chlorine containing compounds: e.g. Halazone, Chloroazodin, Oxychlorosene sodium.

vi) Cationic surfactants: e.g. Benzalkonium chloride, Methylbenzethonium chloride, Benzethonium chloride, Cetyl pyridinium chloride, Chlorhexidine gluconate.

vii) Dyes: e.g. Gentian violet, Basic fuchsine, Methylene blue.

viii) Mercury compounds: e.g. Nitromersol, Thiomersal.

ix) Preservatives

a) p-Hydroybenzoic acid derivatives: e.g. Methylparaben, Propylparaben, Butylparaben, Ethylparaben.

b) Other preservatives: e.g.Chlorobutanol, Benzyl alcohol, Phenylethyl alcohol, Benzoic acid, Sodium benzoate, Sodium propionate, Sorbic acid, Potassium sorbate, Phenyl mercuric nitrate, Phenyl mercuric acetate.

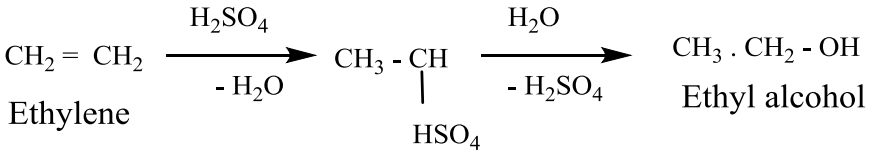
## 2.1 Alcohols and Related Compounds

Alcohols have been used as antiseptic and disinfectants for many years. The most commonly used are ethyl alcohol and isopropyl alcohol. Alcohols exhibit rapid broad-spectrum antimicrobial activity against vegetative bacteria (including mycobacteria), viruses, and fungi but are not sporicidal. Because of the lack of sporicidal activity, alcohols are not recommended for sterilization but are widely used for both hard-surface disinfection and skin antisepsis. Lower concentrations may also be used as preservatives. The activity of alcohols against microorganisms is due to the ability of alcohol to denature important proteins and carbohydrate.

### A. Ethyl alcohol

Ethyl alcohol is a clear, colorless, volatile liquid with a burning taste and characteristic pleasant odor. Commonly it is known as spirit. It is flammable, miscible with water in all proportions and soluble is most organic solvents.

Synthesis

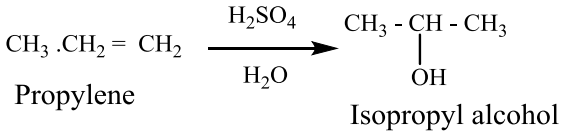



Use: It is used as antiseptic, preservative, mild counter irritant, astringent, rubefacient and mild local anesthetics. It is also used in the practice of pharmacy for the preparation of spirits, tinctures and fluid extracts. Alcohol is an excellent solvent in liquid drug products such as cough syrups, vitamin tonics and others. It is a CNS depressant.

### B. Isopropyl Alcohol

It is a colorless volatile liquid with characteristic odor and slightly bitter taste.

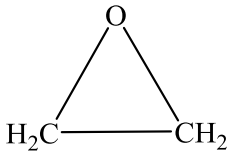
Synthesis




Use: It is used in pharmaceuticals and toiletries as a solvent and preservatives. It is used for the disinfection of hypodermic syringes and needle and as rubbing alcohol, a skin antiseptic.

**C. Ethylene oxide**

It is also called as oxirane. It is a colorless flammable gas with a faintly sweet odour and slightly bitter in taste, liquefies at 12$^{o}$C. The mechanism of the germicidal action of ethylene oxide probably involves the alkylation of functional groups in nucleic acids and proteins by nucleophilic opening of the oxide ring.

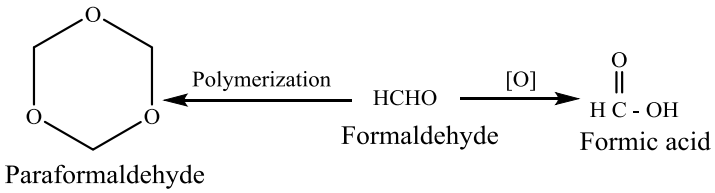



Use: It is used to sterilize temperature sensitive medical equipment and certain pharmaceuticals that cannot be heat sterilized in an autoclave.

**2.2 Aldehydes**

**A. Formaldehyde Solution**

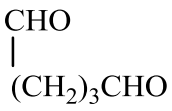
It is a colorless aqueous solution, contains not less than 37% w/v of formaldehyde with added methanol to retard polymerization. Formaldehyde readily undergoes oxidation to formic acid and polymerized to Paraformaldehyde, hence, it must be stored in tightly closed, light-resistant containers. The mechanism of action involves direct non-specific alkylation of nucleophilic functional group in proteins and nucleic acid to form carbinol derivative.




Use: It is used as disinfectant, active against Gram-positive and Gram-negative bacteria, spores and fungi.

**B. Glutaraldehyde Solution**

Glutaraldehyde is a dialdehyde with broad spectrum of activity against bacteria and its spores, fungi and viruses.




1, 5 - Pentanedial

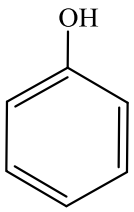
Use: It is used as dilute solution for sterilization of equipment and instruments that cannot be autoclaved. It is used as a disinfectant and sterilant, for endoscopes and surgical equipment and as a fixative in electron microscopy.

**2.3 Phenols and its Derivatives**

A number of phenols are actually more bactericidal than phenol itself. Substitution with alkyl, aryl and halogens in the *p*-position increases bactericidal activity. A straight chain alkyl group enhances bactericidal activity more than branched groups. Alkylated phenols and resorcinol are less toxic than the parent compound. Phenols denature bactericidal proteins at low concentrations, while lysis of bacterial cell membrane occurs at higher concentrations.

**A. Phenol**

It is also known as carbolic acid. It is a colorless to pale pink crystalline material with a characteristic medicinal odor. It is soluble in water, methanol and very soluble in alcohol.




Use: It is used as antiseptic and disinfectant.

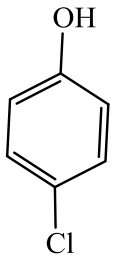
**B. Liquefied Phenol**

It is simply a phenol containing 10% water. The liquid form is convenient for adding phenol to a variety of pharmaceutical preparations, because it can be measured and transferred easily. The water content precludes its use in fixed oils or liquid petroleum because the solution is not miscible with lipophilic ointment bases.

Use: It is used as antiseptic and disinfectant.

**C. *p*-Chlorophenol**

It is a white crystal with strong phenol odor and slightly soluble in water.

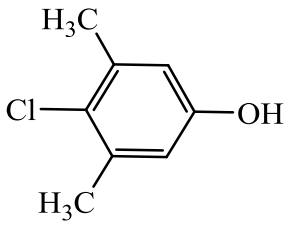



4 - Chloro phenol

Use: It is a disinfectant mostly effective against Gram-negative organisms. It is available as camphorated - *p* - chlorophenol which is used as an external antiseptic and anti-irritant. It is also used as an intermediate in organic synthesis of dyes and drugs.

### D. p-Chloro-*m*-xylenol

It is a white to off-white crystalline powder and soluble in most of the organic solvents.

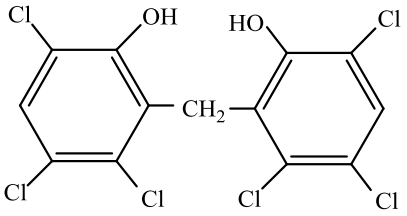



4 - Chloro - 3, 5 - dimethyl phenol

Use: It is a broad spectrum antibacterial and antifungal agent. It is available as shampoo with 2% concentration. It is also used for the treatment of *tinea* and jock itch.

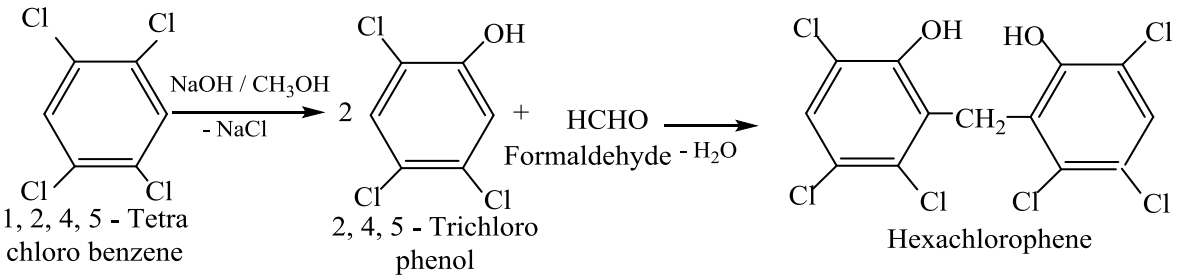
### E. Hexachlorophene

It is a white to light tan white crystalline powder. Insoluble in water, but soluble in alcohol and most of the organic solvents.




2, 2' - Dihydroxy - 3, 5, 6, 3', 5', 6' - hexachloro diphenyl methane

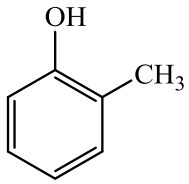
Synthesis



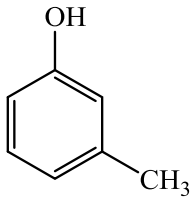
Use: It is used in a concentration of 2 to 3% in soaps, detergent, creams, lotions and shampoos for antiseptic purpose. It is effective against Gram-positive bacteria.

**F. Cresol**

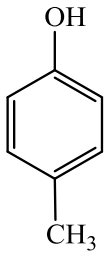
Cresols are chemically methyl phenols. Depending upon the temperature it may be solid or liquid. By long exposure to air, it slowly oxidizes. There are three forms of cresols based on methyl groups substituted on to the benzene ring of a phenol molecule.




2 - Methyl phenol
(*o* - Cresol)




3 - Methyl phenol
(*m* - Cresol)

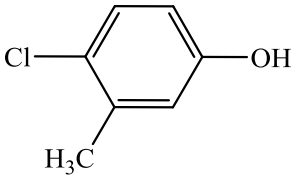



4 - Methyl phenol
(*p* - Cresol)

Use: It is used as antiseptic, disinfectant and deodorant.

**G. Chlorocresol**

It is a chlorinated phenol, forms a colorless amorphous crystal at room temperature. It is slightly soluble in water.

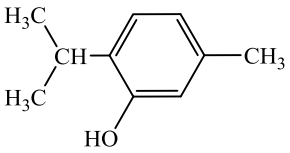



4 - Chloro - 3 - methyl phenol

Use: It is used as antiseptic and preservative.

**H. Thymol**

It is slightly soluble in water at neutral pH. Freely soluble in alcohol and other organic solvent. It is also called as isopropyl-*m*-cresol.

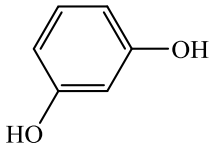


2 - Isopropyl - 5 - methyl phenol

Use: It is used as preservative, anaesthetic and antiseptic in mouth wash. It has mild fungicidal property and is used in dusting powder for the treatment of ringworm infections.

## I. Resorcinol

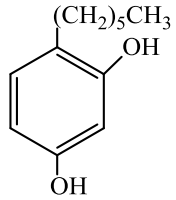
It is a dihydroxy phenol. Chemically it is 1, 3 - isomer of benzenediol. It is readily soluble in water, alcohol and ether but insoluble in chloroform and carbon disulfide.



1, 3 - Dihydroxy benzene

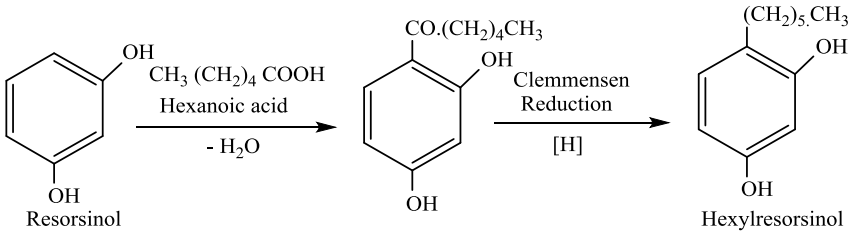
Use: It is used externally as antiseptic and disinfectant.

## J. Hexylresorcinol



4 - (n - Hexyl) - 1, 3 - dihydroxy benzene

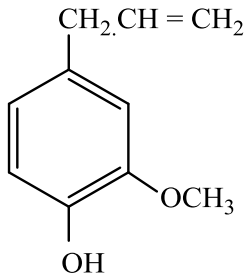
Synthesis



Use: It is an effective antiseptic, possessing both bactericidal and fungicidal properties. It is also used as local anesthetic.

**K. Eugenol**

It is a colorless liquid with an odour of clove. It is slightly soluble in water but is miscible with alcohol and other organic solvents, but dissolve freely in solutions of sodium or potassium hydroxides. It constitutes about 85-90% of clove oil and also occurs in small quantities in cinnamon oil and certain other volatile oils.



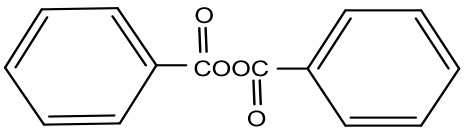

4 - Allyl - 2 - methoxy phenol

Use: It possess both local anesthetic and antiseptic properties and directly applied on to tooth using a piece of cotton to relieve toothaches. It is also used in mouth washes because of its antiseptic property and pleasant taste.

**2.4 Oxidizing Agents**

Oxidizing agents acts as germicide and its activity depends on their ability to liberate oxygen in the host. Most of these agents are inorganic compounds. eg. Hydrogen peroxides, Metal peroxides, Sodium perborate. These agents react in the tissues to generate oxygen and oxygen radicals. Other oxidizing agents, such as $KMnO_4$, denature proteins in microorganism through a direct oxidation reaction. They are effective against anaerobic bacteria and can be used in cleaning contaminated wounds.

**A. Hydrous Benzoyl Peroxide**



Benzoyloxy benzoate

It is a white granular powder. Pure powder form is explosive.

Use: 5 and 10% concentrations are used as keratolytic and keratogenic. It is also used in the treatment of acne.

**B. Carbamide Peroxide**

It is also known as urea peroxide, urea hydrogen peroxide and percabamide. It is slightly soluble in water. It contains approximately 35% of hydrogen peroxide.

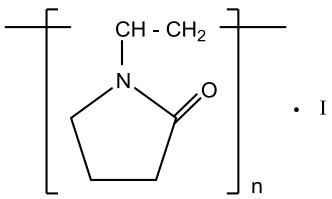
$$\left[NH_2CONH_2\right]_2 \bullet H_2O_2$$

Use: It is used as antiseptic, disinfectant and especially in the treatment of oral ulcerations or in dental care.

**2.5 Halogen-Containing Compounds**

**2.5.1 Iodine Compounds**

**A. Povidone - Iodine**



1 - Vinyl - 2 - pyrrolidinone polymer compound

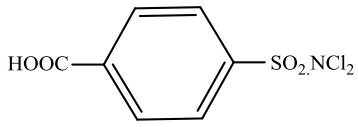
It is a 1 - Vinyl polymeric compound with iodine. It contains 9-12% of available iodine. It is a yellowish-brown amorphous powder, having a slight characteristic odor, soluble in water, alcohol, but insoluble in chloroform, ether, carbon tetrachloride, hexane and acetone.

Use: It kills both Gram-positive and Gram-negative bacteria, fungi, viruses, protozoa and yeasts.

### 2.5.2 Chlorine - Containing Compounds

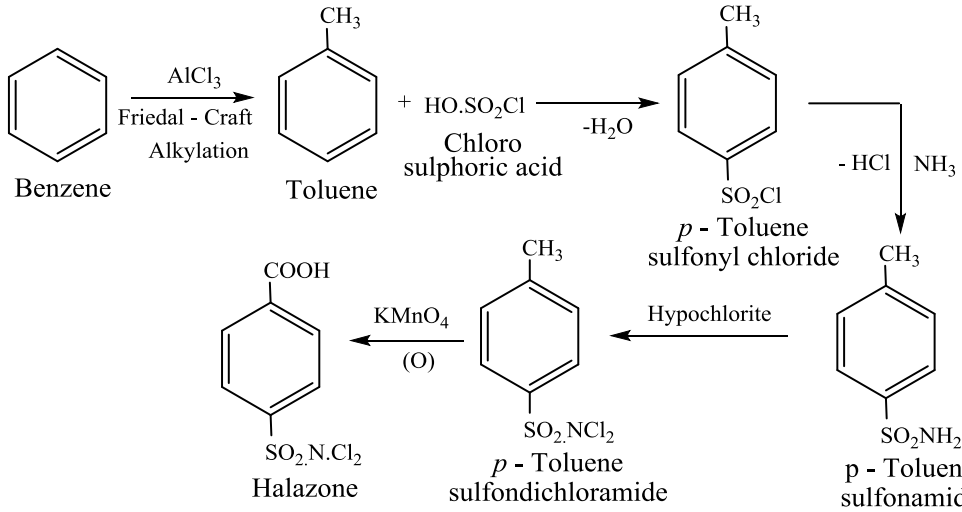
Chlorine and chlorine releasing compounds have been used for disinfection of water.

**A. Halazone**




p - Dichloro sulfamoyl benzoic acid

Synthesis

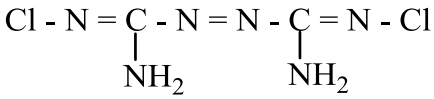



It is a white, crystalline powder having chlorine like odor, slightly soluble in water.

Use: It is used for the disinfection of water as tablets.

**B. Chloroazodin**

It is a synthetic agent. It is also called as azochloramid.

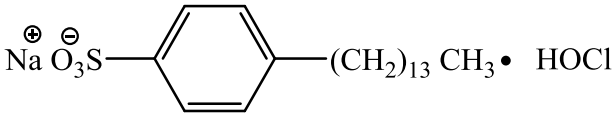


N, N - Dichloroazo dicarbon amidine

Use: It is used as local application of skin, mucosa, nose cavity and topical anti-infective agent.

**C. Oxychlorosene sodium**

It is a stabilized organic compound of hypochloric acid. It is a white water soluble powder with characteristic odour of hypochlorous acid.



Sodium salt of dodecylbenzenesulfonic acid and hypochlorous acid

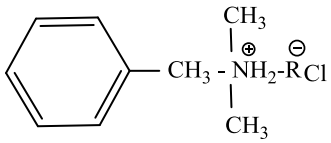
Use: It is used as topical antiseptic in the treatment of localized infection.

**2.6 Cationic Surfactants**

All the cationic surfactants are quaternary ammonium compounds. The cationic surfactants exert a bactericidal action against a broad spectrum of Gram-positive and Gram-negative bacteria and also active against pathogenic species of fungi and protozoa. The bactericidal action of cationic surfactant is slower than that of iodine.

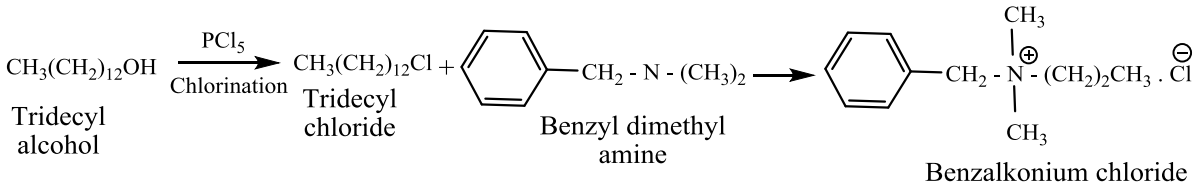
## A. Benzalkonium Chloride

Alkyl benzyl dimethyl ammonium chloride is a mixture of alkyl benzyl dimethyl ammonium chloride of the general formula $[C_6H_5CH_2N\ (CH_3)_2R]^+\ Cl^-$, where R represents a mixture of alkyl chains beginning with $C_8H_{17}$ and extending to higher homologues with $C_{12}H_{25}$, $C_{14}H_{29}$ and $C_{16}\ H_{33}$.



It forms a white or yellowish white thick gel or gelatinous pieces, aromatic odour with very bitter taste. It is freely soluble in water and alcohol.

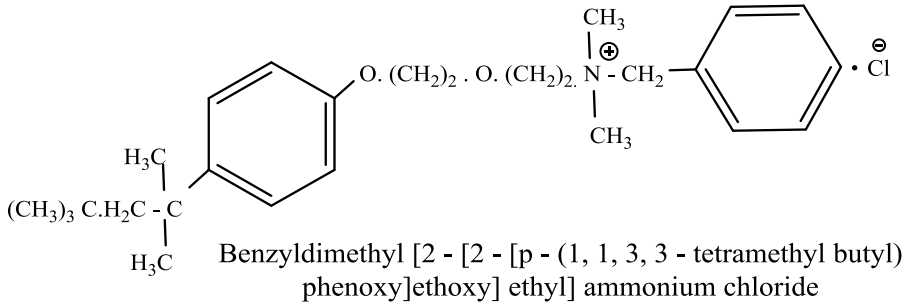
Synthesis




Use: It is a detergent, an emulsifier and wetting agent. It is used as antiseptic for skin and mucous membrane.

## B. Benzethonium Chloride

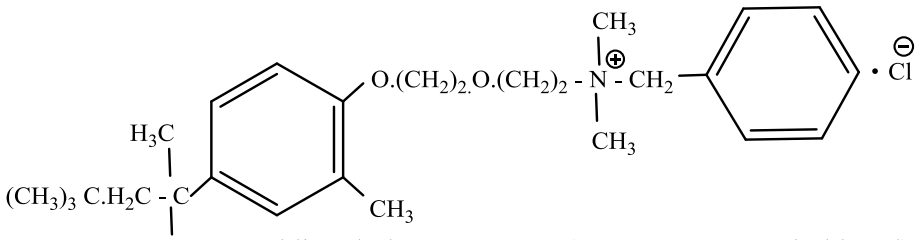
It is a colorless crystalline powder soluble in water, alcohol and most of the organic solvents.




Benzyldimethyl [2 - [2 - [p - (1, 1, 3, 3 - tetramethyl butyl) phenoxy]ethoxy] ethyl] ammonium chloride

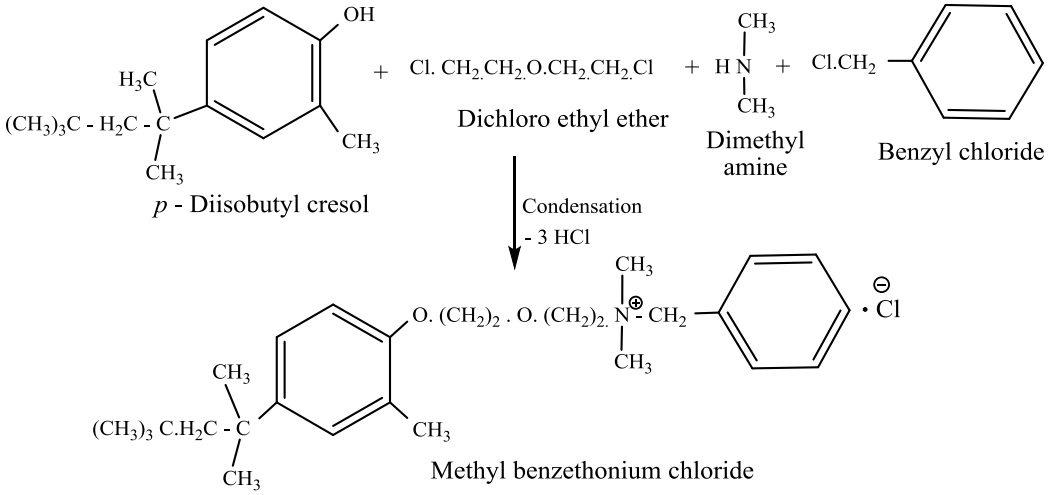
Use: It has surfactant, antiseptic and anti-infective properties. It is used as a topical antimicrobial agent in first aid antiseptics.

### C. Methyl benzethonium chloride



Benzyldimethyl [2 - [2 - [[4 - (1,1,3, 3 - tetramethyl butyl) tolyl] oxy] ethoxy] ethyl] ammonium chloride

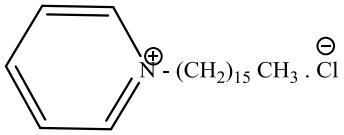
Synthesis




It is a white, hygroscopic crystal with mild odour having bitter taste. It is freely soluble in water and alcohol.

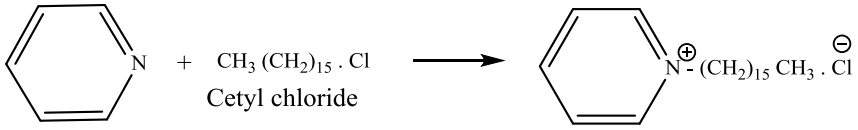
Use: It is used specifically for the treatment of diaper rash in infants caused by *Candida albicans*, which produces ammonia. It is also used as general antiseptic.

## D. Cetylpyridinium Chloride



1- Hexadecyl pyridinium chloride

Synthesis



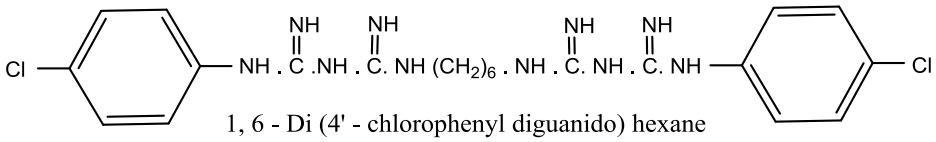

Pyridine

Cetylpyridinium chloride

It is a white powder, very soluble in water and alcohol.

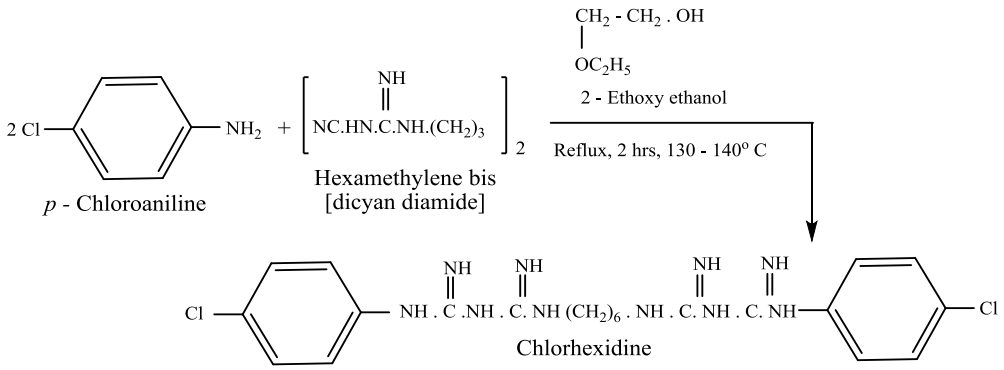
Use: A local anti-infective with surface active and antiseptic properties. It is used in lozenges and mouth washes.

## E. Chlorhexidine



1, 6 - Di (4' - chlorophenyl diguanido) hexane

Synthesis




*p* - Chloroaniline

Hexamethylene bis [dicyan diamide]

Chlorhexidine

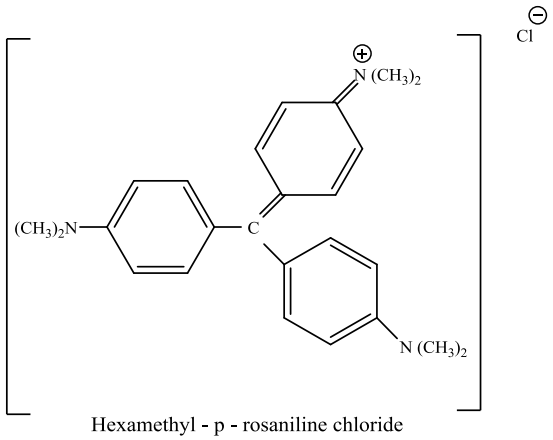
Use: It is bactericidal to both Gram-positive and Gram-negative bacteria, but it is not active against acid-fast bacteria, spores or viruses. It has been used for topical as preoperative skin disinfection, wound irrigation, mouthwashes and general sanitization.

## 2.7 Dyes

Organic dyes are used very widely as anti-infective agent. Cationic dyes for eg. Gentian violet, Basic fuchsin and Methylene blue have limited use as anti-infective agent. These cationic dyes are active against Gram-positive bacteria and many fungi: but Gram-negative bacteria are resistant.

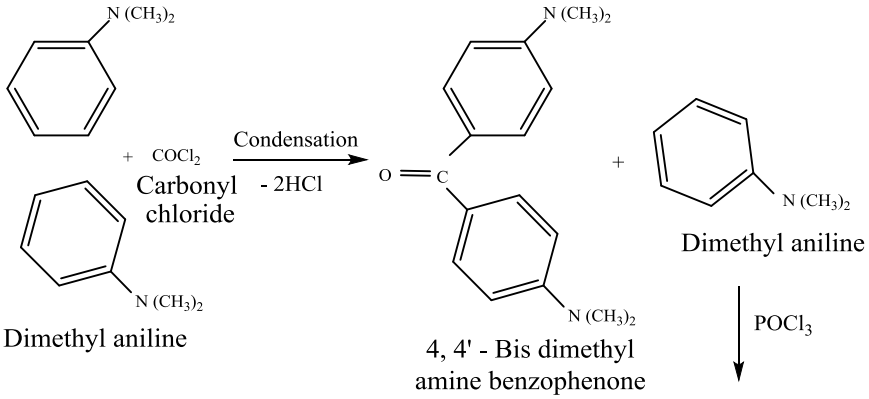
### A. Gentian Violet (Crystal Violet)

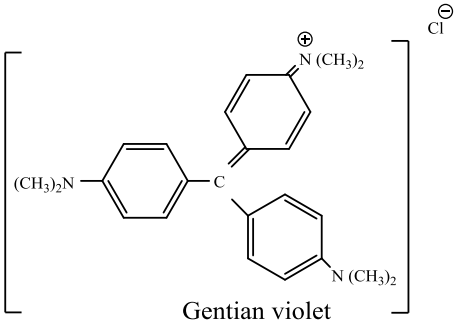
It occurs as green powder, soluble in water, alcohol, but insoluble in non-polar organic solvent.




Hexamethyl - p - rosaniline chloride

Synthesis

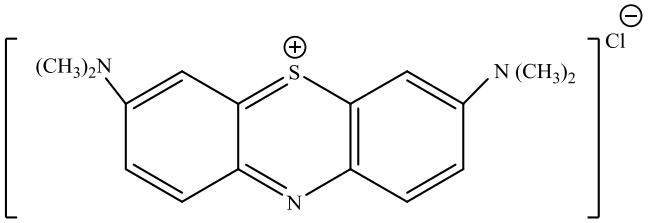





Gentian violet

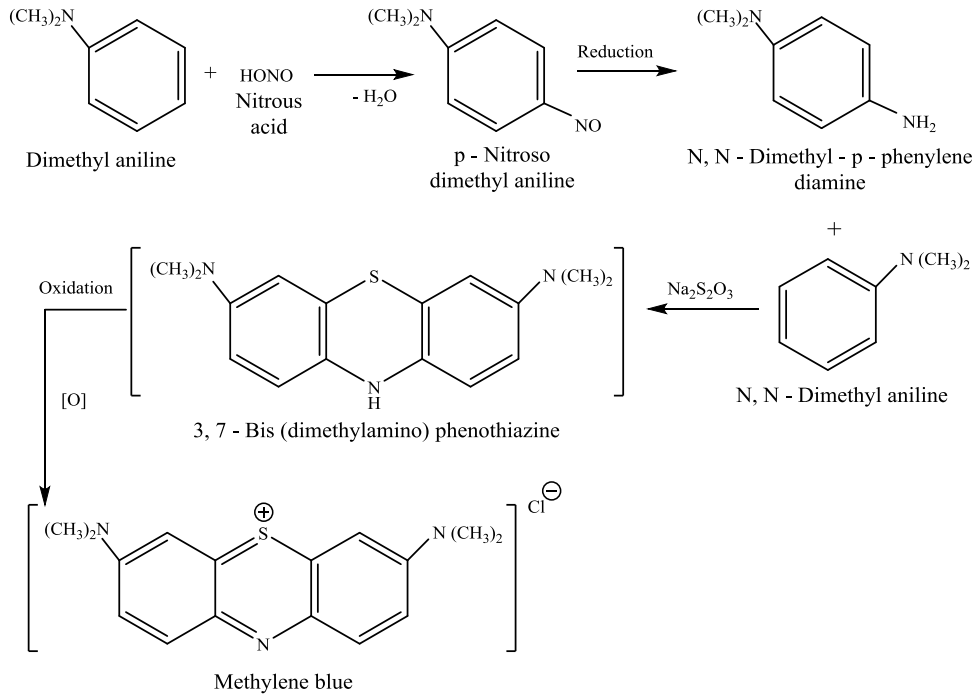
Use: It is used as antiseptic.

## B. Methylene Blue




3, 7 - Bis (dimethyl amino) phenazathionium chloride

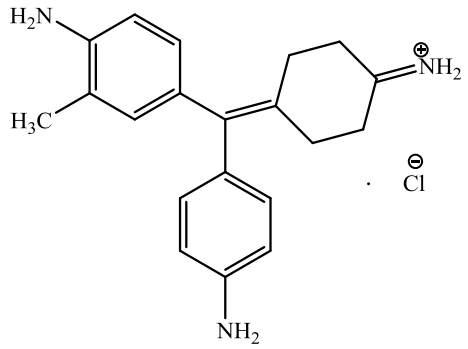
Synthesis



Use: It has antiseptic properties. It is used in the treatment of methemoglobinemia.

### C. Basic Fuchsin (Rosaniline Hydrochloride)

It occurs as green crystalline powder, soluble in water and alcohol, but insoluble in ether. It is a component of Carbol-fuchsin solution.



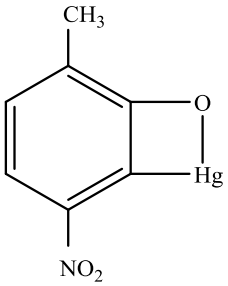

4 - [(4 - Amino phenyl) - 4 - iminocyclo - 2, 5 - dienylidene) methyl] aniline hydrochloride

Use: It is used in the treatment of fungal infection especially ringworm and athlete's foot.

## 2.8 Mercury Compounds

Mercury and its derivatives have been used as antiseptic and disinfectants. The antibacterial action of mercury compound is due to their reaction with sulfhydryl (-SH) groups in enzymes to form covalent compounds of the type R-S-Hg-R'.

### A. Nitromersol

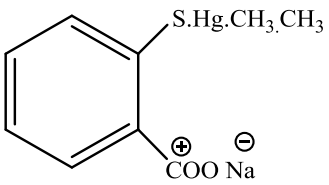



3 - (Hydroxy mercuri) - 4 - nitro - o - cresol

It occurs as yellow powder, insoluble in water, sparingly soluble in alcohol and organic solvent. It is non-irritating and non-staining.

Use: It is used in the treatment of ocular infection.

**B. Thimerosal**




[o - (Carboxy phenyl)thio] ethyl mercury sodium salt

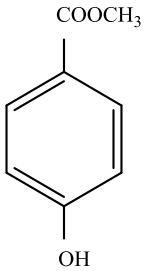
It is a cream-colored powder, soluble in water. It is also non-staining and non-irritating.

Use: It is used as disinfectant and preservative.

**2.8 Preservatives**

It is a substance added to various pharmaceutical dosage forms and cosmetic preparations to prevent or inhibit microbial growth. An ideal preservative would be effective at low concentrations against all possible micro-organism, be non-toxic and compatible with other constituent of the preparation and be stable for the shelf life of the preparation.

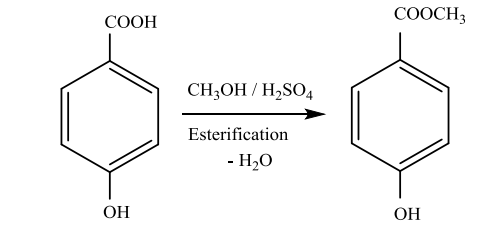
**A. Methylparaben**




Methyl - p - hydroxy benzoate

It is a white crystalline powder, characteristic odor, soluble in water and alcohol, slightly soluble in non-polar organic solvent.

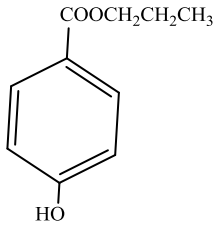
Synthesis




p - Hydroxy benzoic acid Methyl paraben

Use: It is used as antiseptic and preservative in various pharmaceutical preparations. It is also used in cosmetic preparation containing vegetable and animal fats and oils that are susceptible to decomposition.

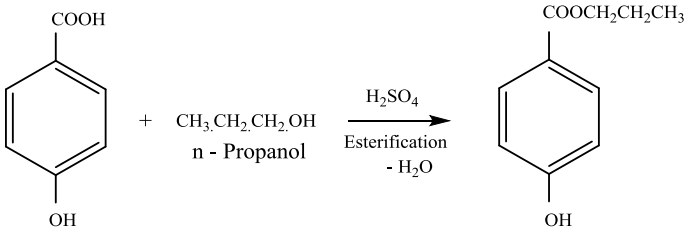
**B. Propylparaben**




Propyl - p - hydroxy benzoate

It occurs as a white crystalline powder, slightly soluble in water, but soluble in most of the organic solvents.

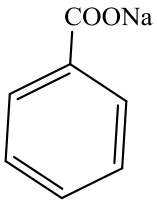
Synthesis




p - Hydroxy benzoic acid Propylparaben

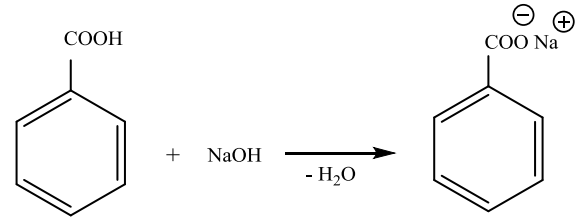
Use: It is used as a preservative, primarily to retard yeast growth.

### C. Sodium Benzoate




It is a white crystalline solid, soluble in water and alcohol.

Synthesis




Use: Extensively used as a food and pharmaceutical preservatives. It is not a bactericidal but only a bacteriostatic. It also possesses fungistatic activity.