Antimicrobial and antifungal preservatives

•compounds necessary for protection of medicinal preparations against unwanted microorganisms being able to decompose active ingredients and/or other excipients or evoke dangerous microbial contamination (vaccines)

Outline of the most often used structural groups of preservatives

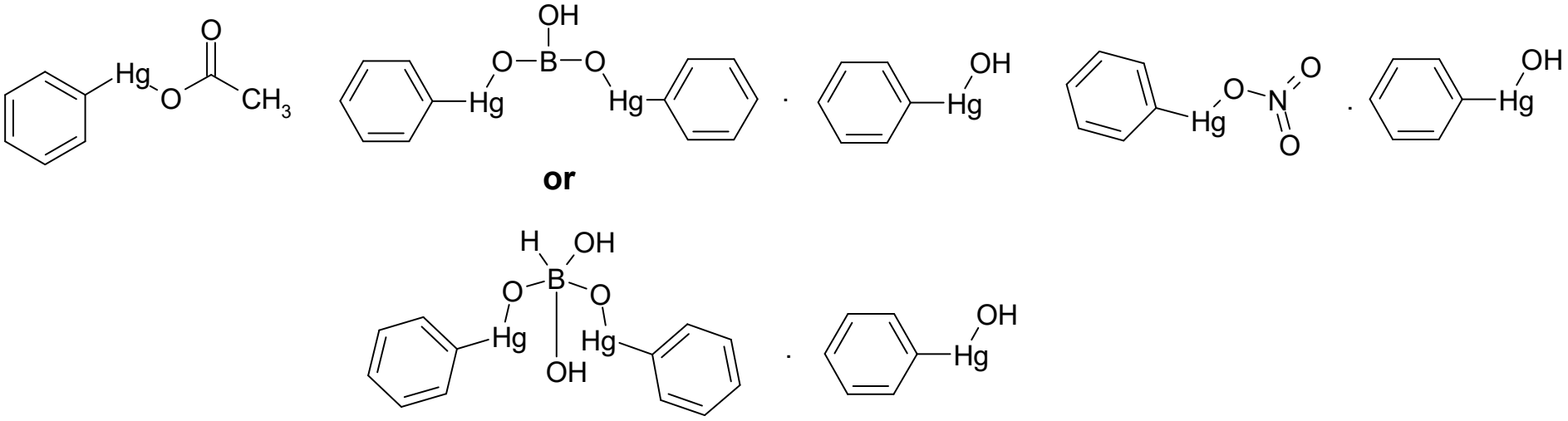
1. Organic compounds of mercury
2. Alcohols and phenols
3. Aldehydes and their precursors
4. Carboxylic acids
5. Quarternary ammonium salts

1.Organic compounds of mercury

- preservation of sterile ocular and parenteral preparations, mainly vaccines in multi-dose bottles
- one of the last rests of heavy metals compounds, formerly widely spread in medicine
- much less toxic than soluble inorganic mercuric salts ($HgCl_2$)
- bactericidal and fungicidal effect, slightly to spores
- mode of action: interaction with -SH groups of microbial proteins

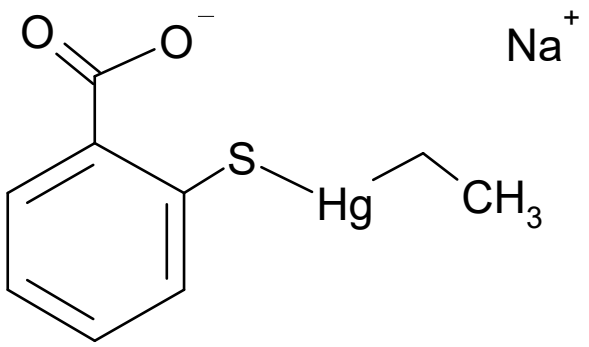
1.1 Phenylmercuric salts

- covalent salts of inorganic or caboxylic acids with phenylmercuric moiety
- mixtures of such salts with phenylmercuric hydroxide are often acceptable by many pharmacopoeias



Phenylmecuric acetate	Phenylmercuric borate	Phenylmercuric nitrate
Phenylhydrargyri acetas	*Phenylhydrargyri boras*	*Phenylhydrargyri nitras*
	Famosept ®	

1.2 Thiomersal



syn. thimerosal, merthiolate
sodium 2-(ethylhydrargyriumsulfanyl)benzoate
sodium 2-(ethylmercurithio)benzoate
sodium ethylmerkurithiosalicylate

•typically preservation of multi-dose vaccines

•relationship between autism of some of vaccinated children and

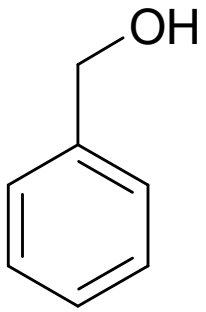
thiomersal formerly discussed, but no evidence

•stepwise abandoned

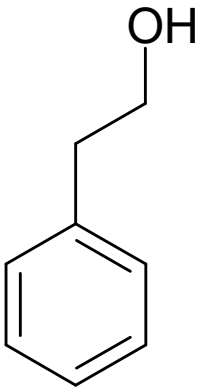
2. Alcohols and phenols

2.1 Alcohols

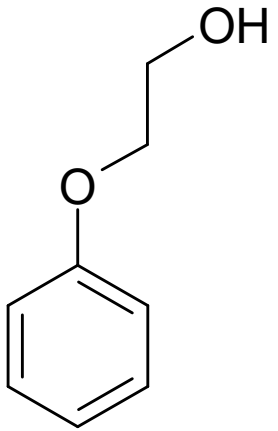
•preservation ability of short-chain alconols like ethanol and propane-2-ol is usable only if their concentration in a preparation is satisfactory (cca 20 % for ethanol); typical preservatives are aromatic-aliphatic alcohols with orderly lower active concentrations



benzyl alcohol
phenylmethanol
Alcohol benzylicus PhB



phenethyl alcohol
2-phenylethan-1-ol

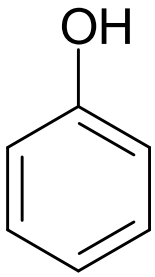


phenoxyethanol
2-phenoxyethan-1-ol
Phenoxyethanolum PhB

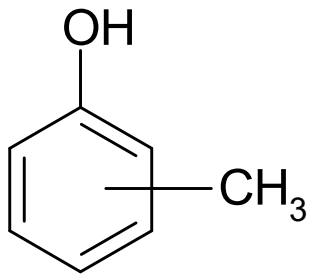
•parenterals, inj. radiopharmaceutics

- preservation of vaccines and topical preparations

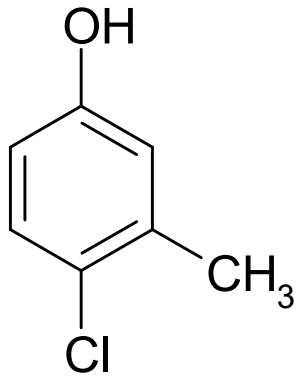
2.2 Phenols



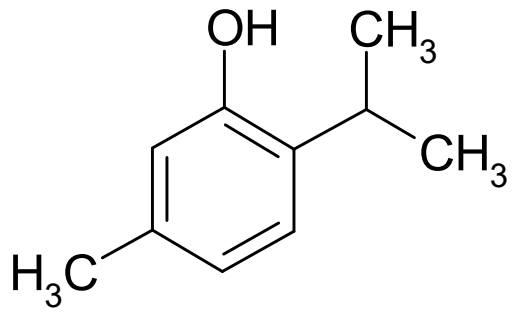
phenol
Phenolum EP
Phenolum liquefactum PhB contains 10 % water
•inactivation and preservation of live vaccines
•preparation *Solutio Galli-Valerio PhB* for preservation of medical instruments



cresols
2-, 3-, 4-methylphenol
Cresolum crudum PhB
= mixture of all 3 isomers
Metacresolum PhB



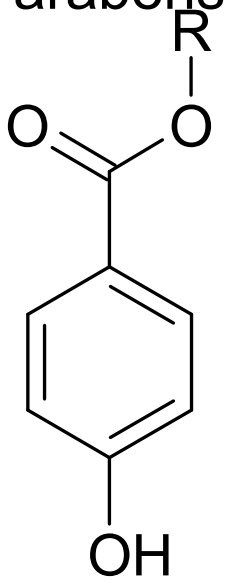
chlorocresol
4-chloro-3-methylphenol
Chlorocresolum PhB



thymol
2-isopropyl-5-methylphenol
Thymolum PhB

2.2 Phenols (continued)

Parabens



alkyl 4-hydroxybenzoates

•originally patented by Theodor Sabalitschka for food preservation in 1926

R = C_nH_{2n+1} most often $1 \geq n \geq 5$

•mainly linear, from branched R = *iso*-C_4H_7 in cosmetics

Methyl- butylparabenum EP; also sodium salts: *Methyl- propylparabenum natricum*

•preservation of external and also p.o. preparations: *Aqua conservans PhB* 0.67 % MP + 0.33 % PP

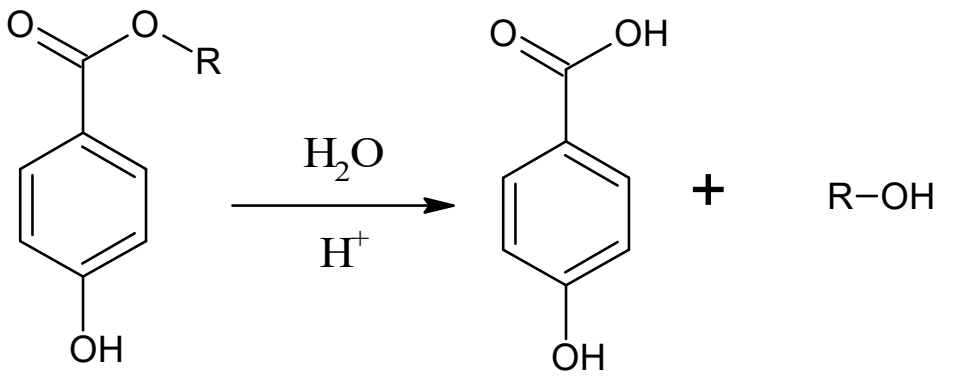
•active in acid, neutral, and alkaline media

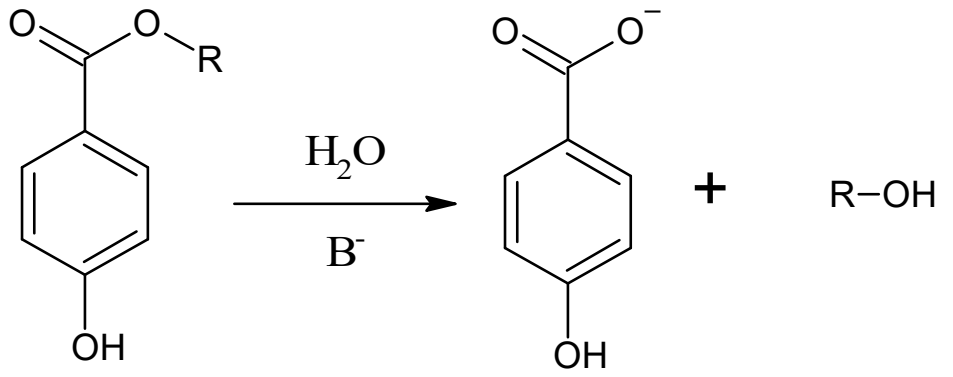
•antifungl activity: R = -CH_3 more active against moulds, R = -C_3H_7 against yeasts

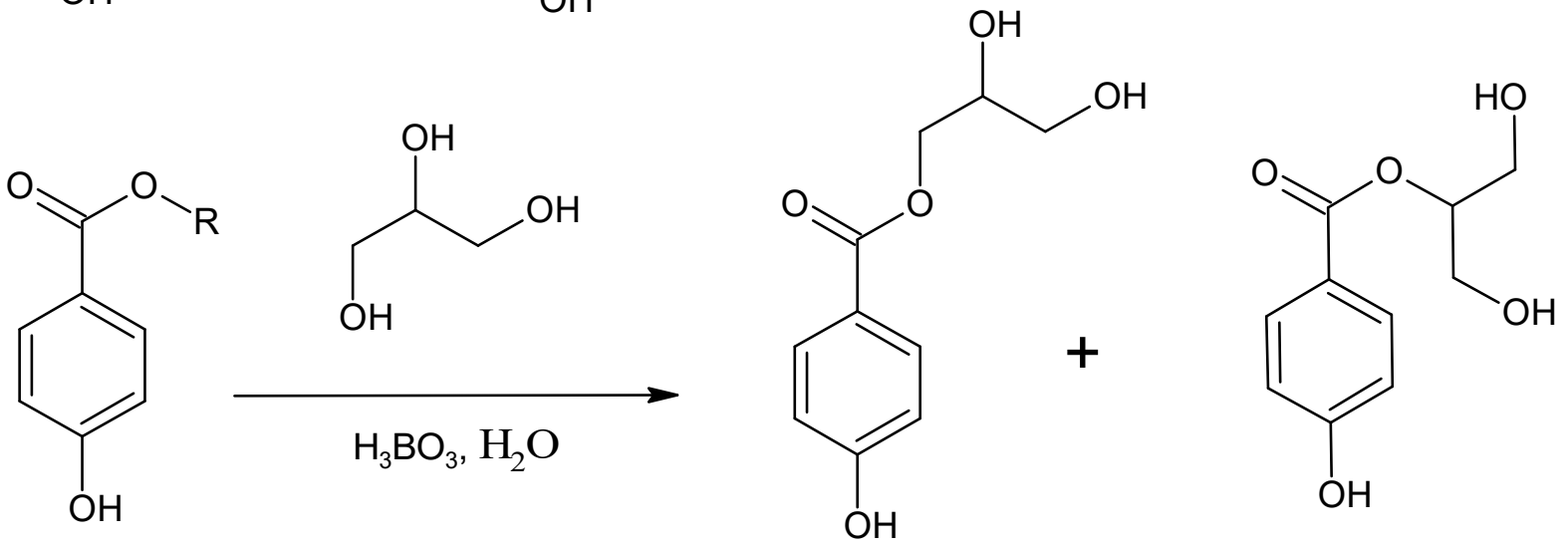
•antibacterial activity increaces with chain length and lipophilicity

•less suitable for foods, weak local anesthetic activity (isosterism with 4-aminobenzoates) lowering taste (but used)

Stability and decomposition reactions of parabens

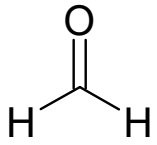






•runs in *Solutio Jarisch* in its traditional composition

3. Aldehydes and their precursors



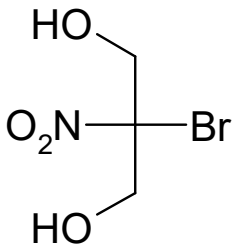
formaldehyde

methanal

Formaldehydum PhB

•40% solution for preservation of anatomic preparations (formaline)

•preparation: *Sol. Galli-Valerio PhB*



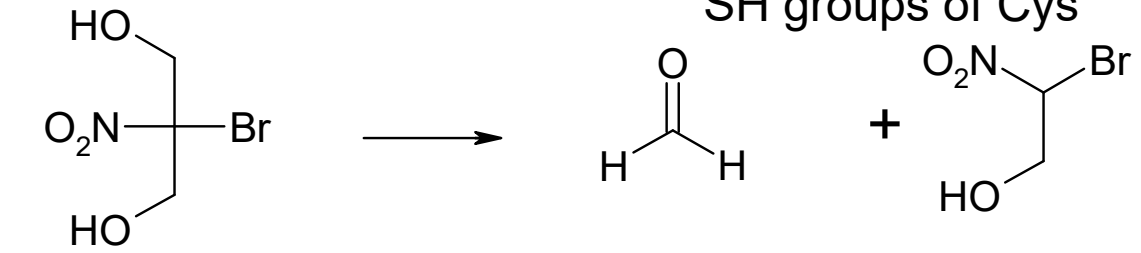
bronopol

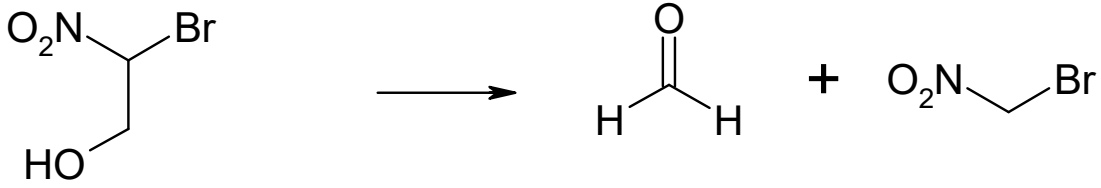
2-brom-2-nitro-1,3-propandiol

•first prepared by Henry in 1898

•antimicrobial aditive in external preparations and in cosmetics

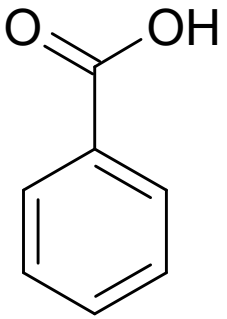
•self mode of action: reaction with -SH groups of Cys



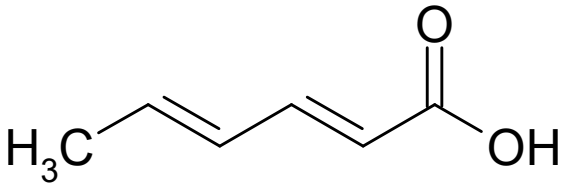


•common mode of action of aldehydes: denaturation of superficial cell membrane proteins by forming of Schiff bases at free ε-amino groups of Lys

4. Carboxylic acids

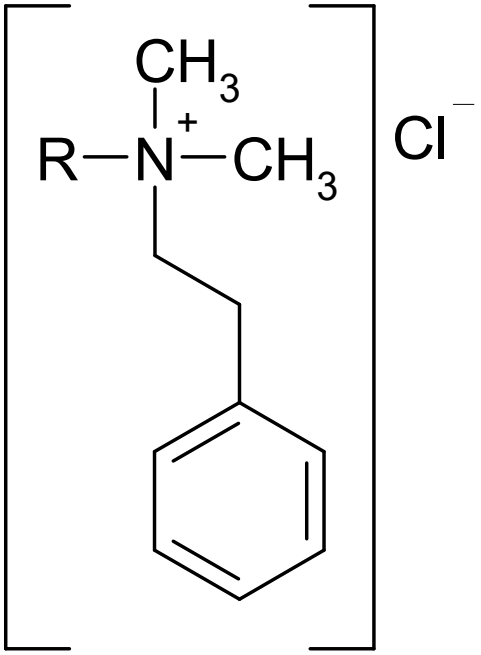


benzoic acid
benzenecarboxylic acid
Acidum benzoicum PhB
•active at pH ≤ 7.3



sorbic acid
(E,E)-hexa-2,4-dienic acid
Acidum sorbicum PhB

5. Quaternary ammonium salts



R = C_8H_{17}-$C_{18}H_{37}$ (mixture)

alkylbenzyldimethylammonium chloride

benzalkonium chloride

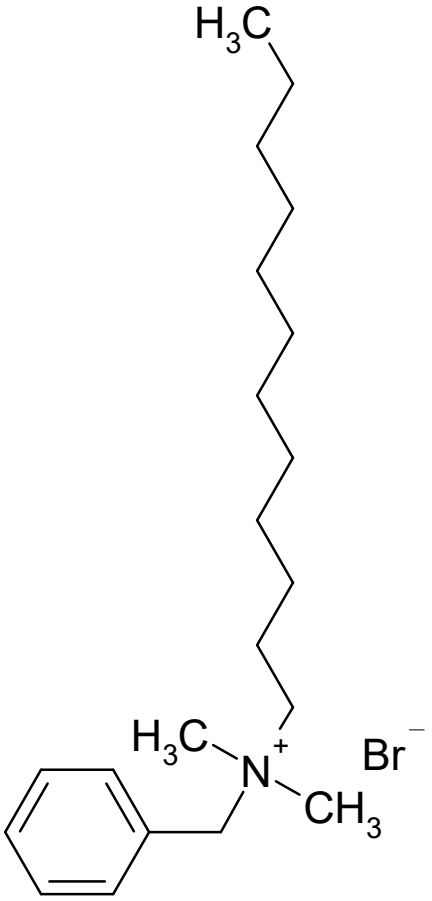
Benzalkonii chloridum EP

•preservation of eye drops

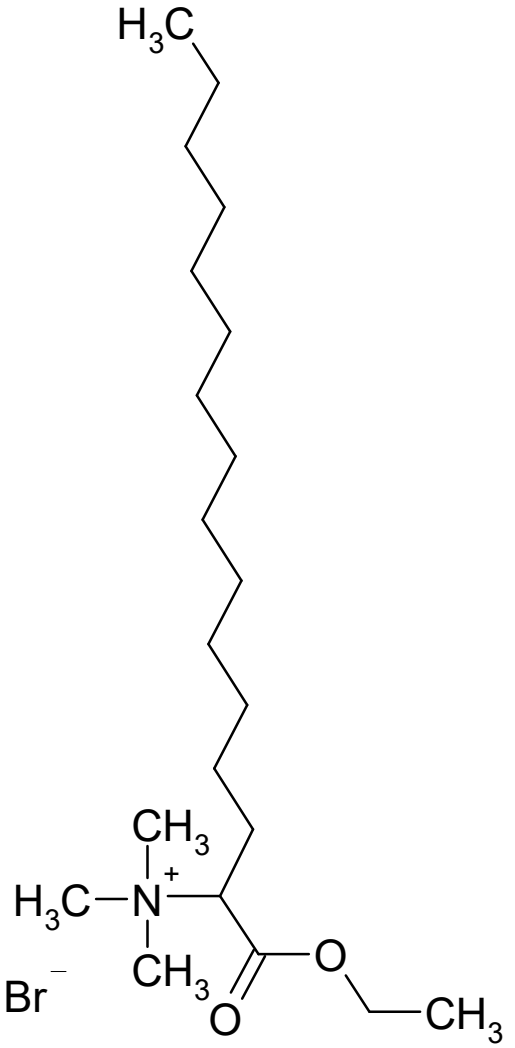
•mode of action: removing of superficial proteins from cellular membrane of microorganisms

•active against bacterie, not against fungi

Quaternary ammonium salts continued



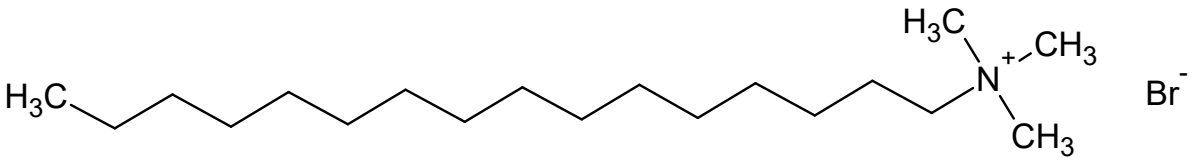
benzododecinium bromide
Ajatin®



carbethopendecinium bromide
Septonex®

- antimicrobial preservatives
- disinfectants, antiseptics
- tensides, emulsifiers

Quaternary ammonium salts continued



cetrimonium bromide
N,N,N-trimethyl-1-hexadecanaminium bromide