

## 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

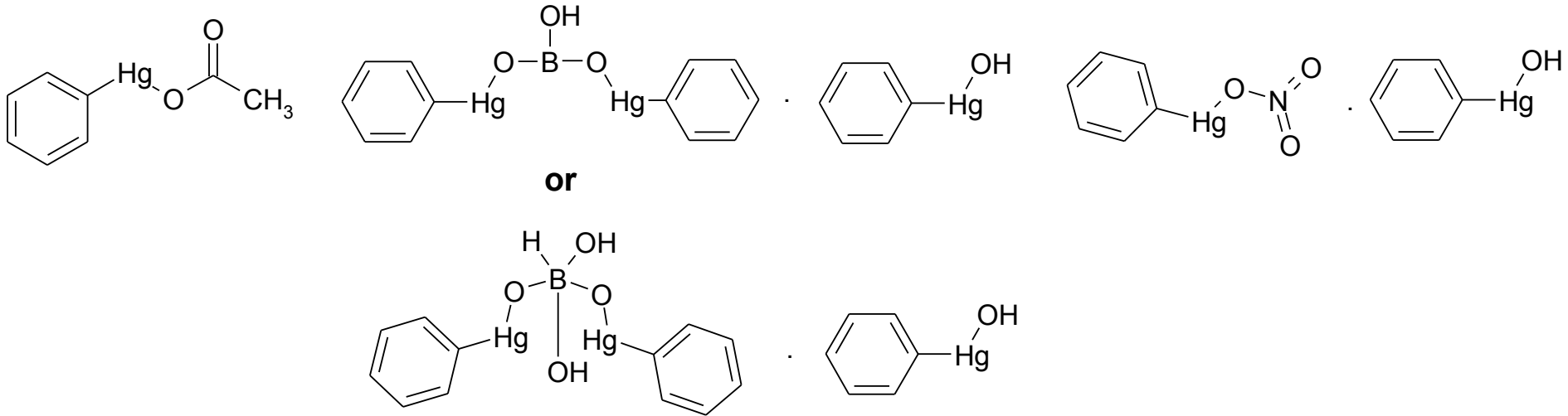
1. Organic compounds of mercury
2. Alcohols and phenols
3. Aldehydes and their precursors
4. Carboxylic acids
5. Quarternary ammonium salts

## 1. Organic compounds of mercury

- preservation of sterile ocular and parenteral preparations, namely 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 ( $\text{HgCl}_2$ )
- 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 carboxylic acids with phenylmercuric moiety
- mixtures of such salts with phenylmercuric hydroxide are often acceptable by many
- pharmacopoeias



Phenylmercuric acetate

Phenylmercuric borate

Phenylmercuric nitrate

*Phenylhydrargyri acetas*

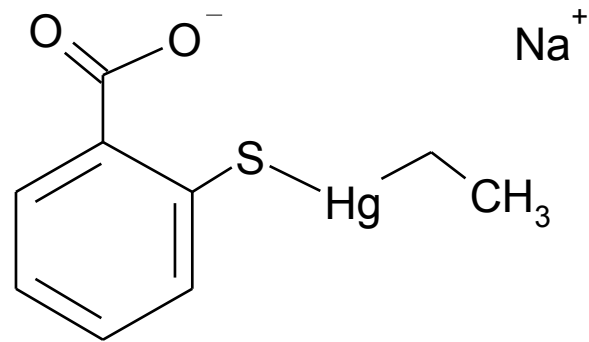
*Phenylhydrargyri boras*

*Phenylhydrargyri nitras*

Famosept<sup>®</sup>

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## 1.2 Thiomersal



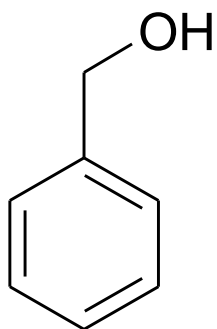
syn. thimerosal, merthiolate  
sodium 2-(ethylhydrargyriumsulfanyl)benzoate  
sodium 2-(ethylmercurithio)benzoate  
sodium ethylmerkurithiosalicylate

- typically preservation of multi-dose vaccines
- possible relationship between autism of some of vaccinated children and thiomersal discussed, but no evidence
- stepwise abandoned

## 2. Alcohols and phenols

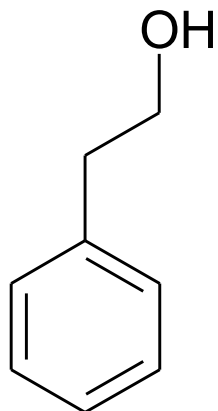
### 2.1 Alcohols

- preservation ability of short-chain alcohols 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

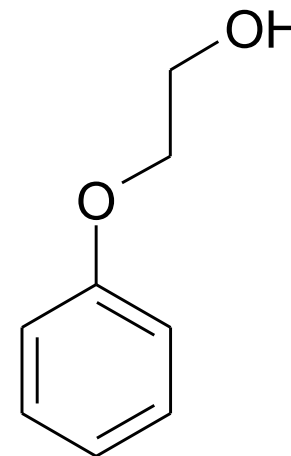


benzyl alcohol  
phenylmethanol

*Alcohol benzylicus* ČL 2005



phenethyl alcohol  
2-phenylethan-1-ol



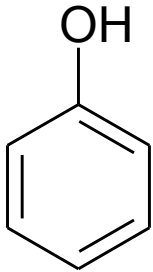
phenoxyethanol  
2-phenoxyethan-1-ol

*Phenoxyethanolum* ČL2005

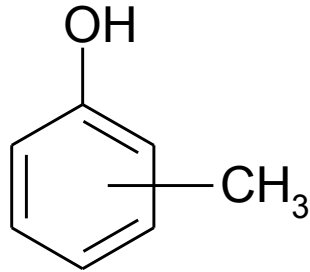
- parenteralia, inj. radiopharmaceutics

- preservation of vaccines and topical preparations

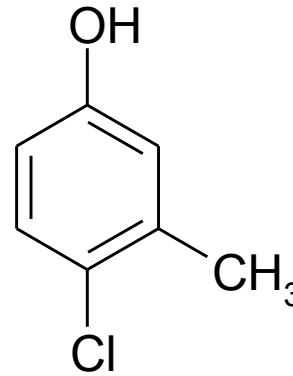
## 2.2 Phenols



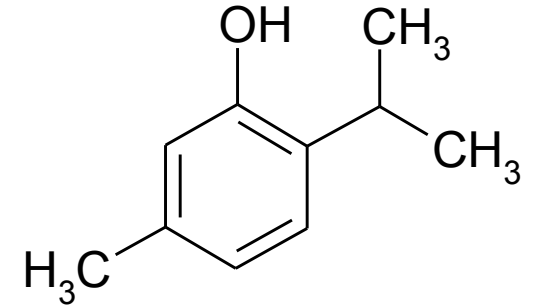
phenol  
*Phenolum* ČL 2009  
*Phenolum liquefactum*  
ČL 2009 contains 10  
% water  
•inactivation and  
preservation of live  
vaccines  
•preparation *Solutio*  
*Galli-Valerio* ČL 2009  
for preservation of  
medical instruments



cresols  
2-, 3-, 4-methylphenol  
*Cresolum crudum* ČL  
2009 = mixture of all 3  
isomers  
*Metacresolum* ČL  
2009



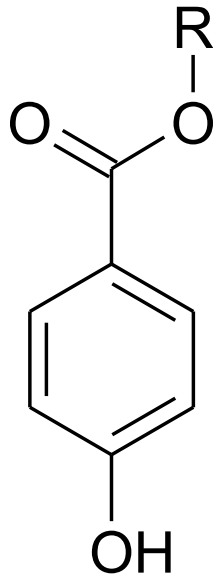
chlorocresol  
4-chloro-3-methylphenol  
*Chlorocresolum* ČL 2009



thymol  
2-isopropyl-5-methylphenol  
*Thymolum* ČL 2009

## 2.2 Phenols (continued)

### Parabens



alkyl 4-hydroxybenzoates

$R = C_n H_{2n+1}$  most often  $1 \leq n \leq 5$

• mainly linear, from branched  $R = iso-C_4 H_7$  in cosmetics

*Methyl- butylparabenum* ČL 2009; also sodium salts: *Methyl- propylparabenum natricum*

• preservation of external and also p.o. preparations: *Aqua conservans* ČL 2009 0,67 % MP + 0,33 % PP

• active in acid, neutral and alkaline media

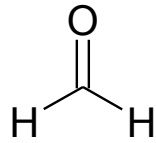
• antifungal activity:  $R = -CH_3$  more active against moulds,  $R = -C_3 H_7$  against yeasts

• antibacterial activity increases with chain length and lipophilicity

• less suitable for foods, slight local anesthetic activity lowering taste (but used)



### 3. Aldehydes and their precursors

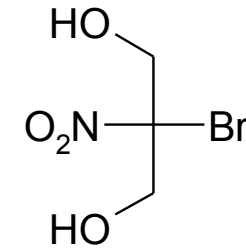


formaldehyde

methanal

*Formaldehydum* ČL 2009

•preparation: *Sol. Galli-Valerio* ČL 2009



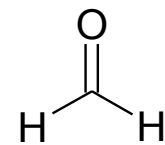
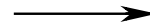
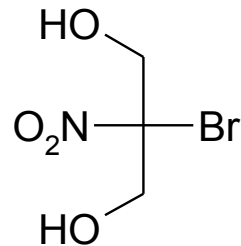
bronopol

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

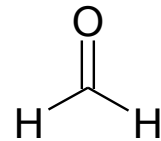
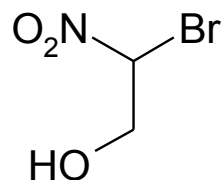
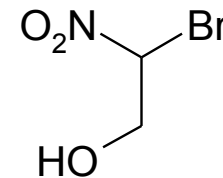
•first prepared by Henry in 1898

•antimikrobiale aditive in external preparations and in cosmetics

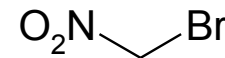
•self mode of action: reaction with -SH groups of Cys



+

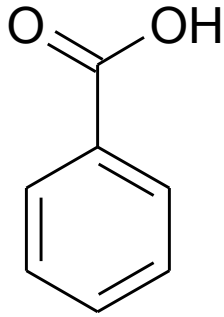


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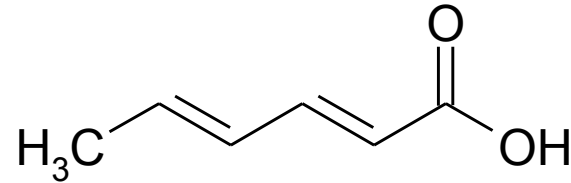


•common mode of action of aldehydes: denaturation of superficial proteins by forming of Schiff bases from free amino groups

## 4. Carboxylic acids

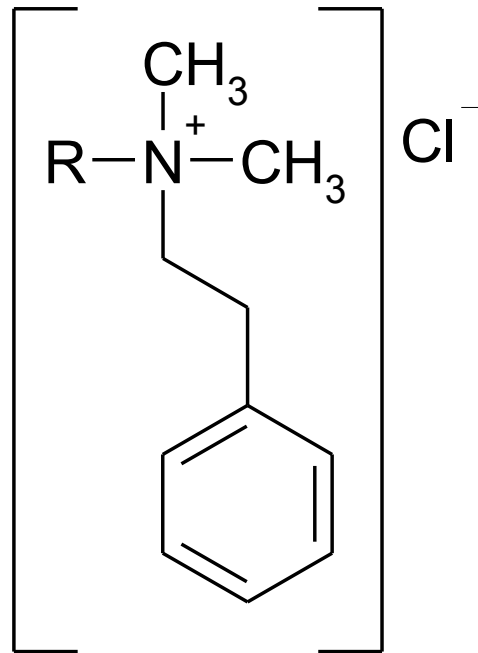


benzoic acid  
benzenecarboxylic acid  
*Acidum benzoicum* ČL 2009  
•active for  $\text{pH} \leq 7.3$



sorbic acid  
(E,E)-hexa-2,4-dienic acid  
*Acidum sorbicum* ČL 2009

## 5. Quarternary ammonium salts



R = C<sub>8</sub>H<sub>17</sub>-C<sub>18</sub>H<sub>37</sub> (mixture)

alkylbenzyltrimethylammonium chloride

benzalkonium chloride

*Benzalkonii chloridum* ČL 2009

- eye drops

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