

## Antioxidants

= compounds preventing oxidation changes of drugs or other PE

- for activity must be dissolved  $\Rightarrow$  classified into **water soluble** and **fat soluble**
- compounds easily oxidizable, and/or catching or scavenging free radicals with shorter half-life
- oxidizing agents:  $O_2$ ,  $O_3$ ,  $\bullet OH$ ,  $\bullet OOH$  and other reactive oxygen (and nitrogen) species [RO(N)S]
- heavy metal cations are oxidation catalyzers ( $Fe^{2+/3+}$ ,  $Cu^{2+}$  ...)  $\Rightarrow$  chelating agents act as synergists of antioxidants

## Aqueous phase antioxidants

### Inorganic salts

$\text{Na}_2\text{SO}_3$ ,  $\text{K}_2\text{SO}_3$  - pH of solution approx. 9

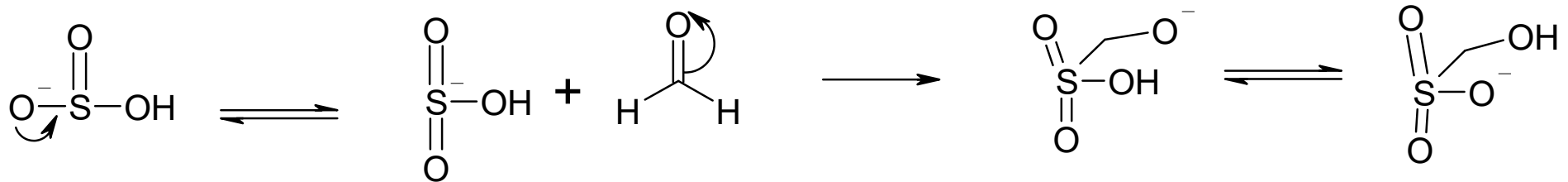
$\text{NaHSO}_3$ ,  $\text{KHSO}_3$ ,  $\text{Na}_2\text{S}_2\text{O}_5$ ,  $\text{K}_2\text{S}_2\text{O}_5$  – solution pH approx. 4

- chem. and physiol. not completely indifferent
- unpleasant taste and smell  $\Rightarrow$  unsuitable for p.o. drug forms

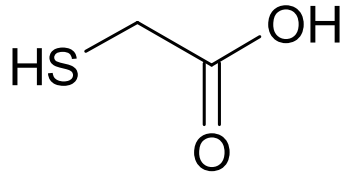
### Organic sulfur compounds

sodium hydroxymethanesulfinic acid = “sodium formaldehydesulfoxylate”

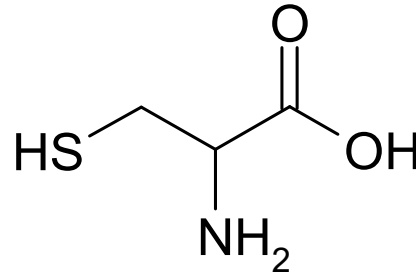
$\text{HOCH}_2\text{SO}_2^- \text{Na}^+$  Rongalit<sup>®</sup>, Leptacit<sup>®</sup>



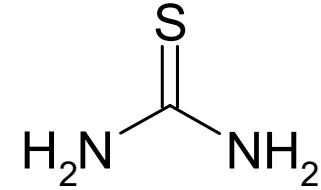
Aqueous phase antioxidants  
Organic sulfur compounds



thioglycolic acid



cysteine

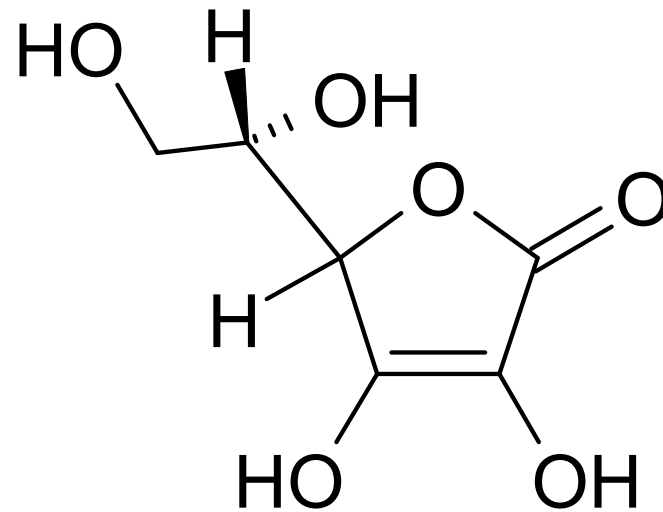


thiourea

•suspected cancerogen

- for unpleasant organoleptic properties unsuitable for p.o. and topic preparations
- usage in concentrations 0.05 – 0.15 %

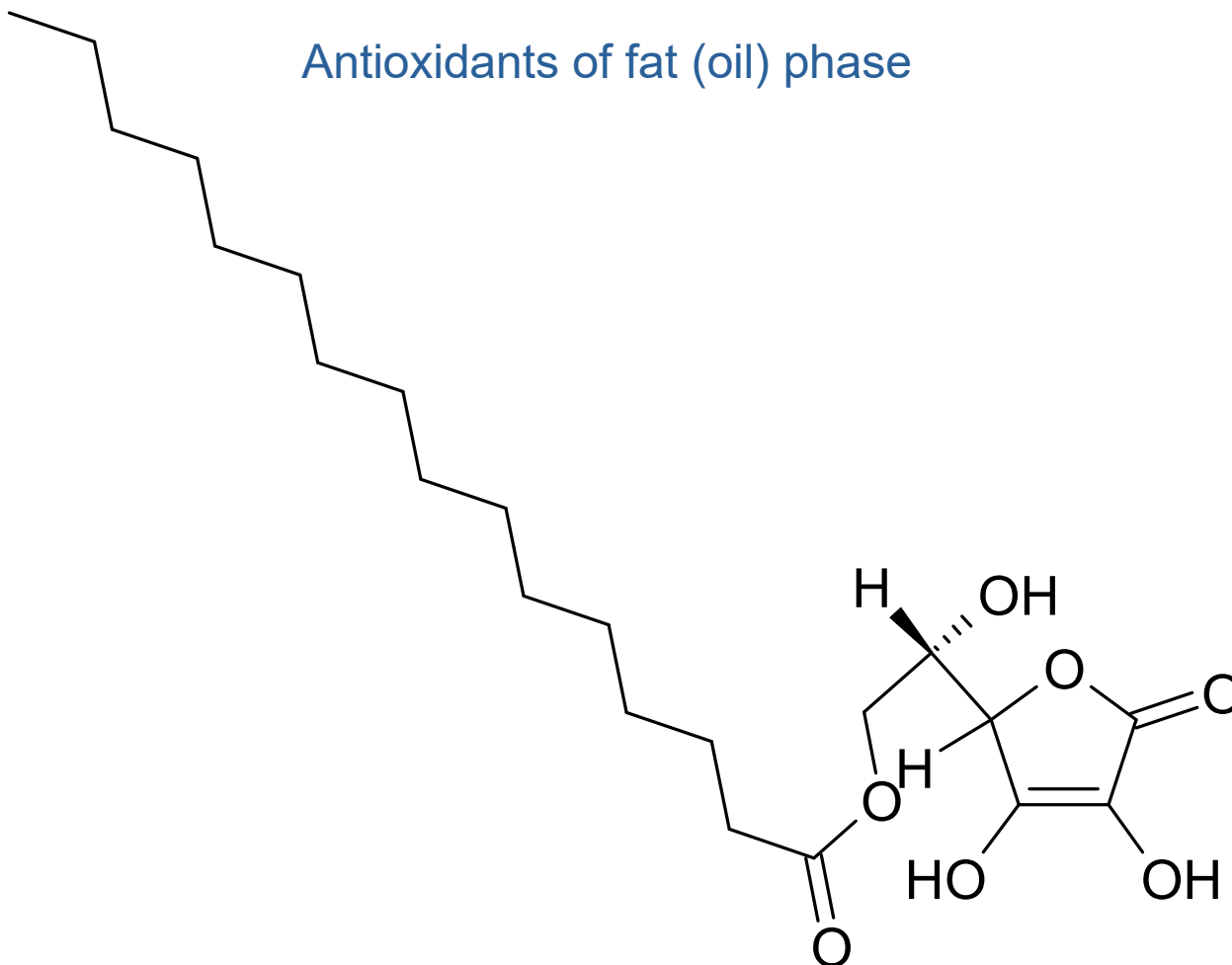
## Ascorbic acid



L-ascorbic acid = 2,3-didehydro-L-*threo*-hexono-1,4-lactone

- antioxidant of aqueous phase of liquid preparations and drugs
- acts prooxidatively with heavy metal cations including  $\text{Zn}^{2+}$

## Antioxidants of fat (oil) phase

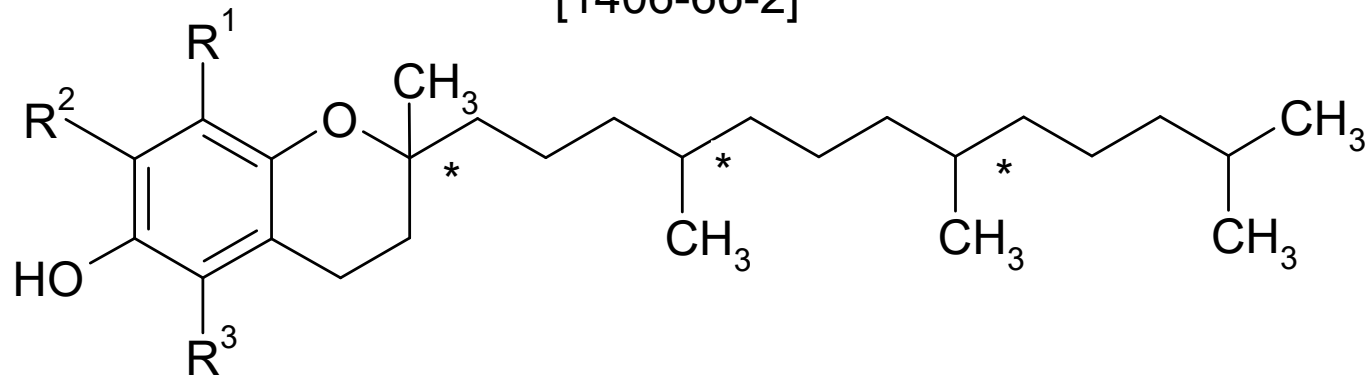


**ascorbyl palmitate** = 6-palmitoyl-L-ascorbic acid = 3-oxo-L-gulofuranolacton-6-palmitate = *Ascorbylis palmitas* PhEur = E304, [137-66-6]

- stabilization of oils in p.o. drug forms and food, stabilization of drugs sensitive to O<sub>2</sub>
- combination with tocopherols is synergic

$$\log P_{o/w} = 1.9$$

Tocopherols  
[1406-66-2]



**$\alpha$ -tocopherol**  $R^1 = R^2 = R^3 = \text{CH}_3$  vitamin E, lowest activity as the antioxidant,  $\log P_{o/w} = 12.18$

**$\beta$ -tocopherol**  $R^1 = R^3 = \text{CH}_3$ ,  $R^2 = \text{H}$  the most resistant against heat and alkalies,  $\log P_{o/w} = 11.63$

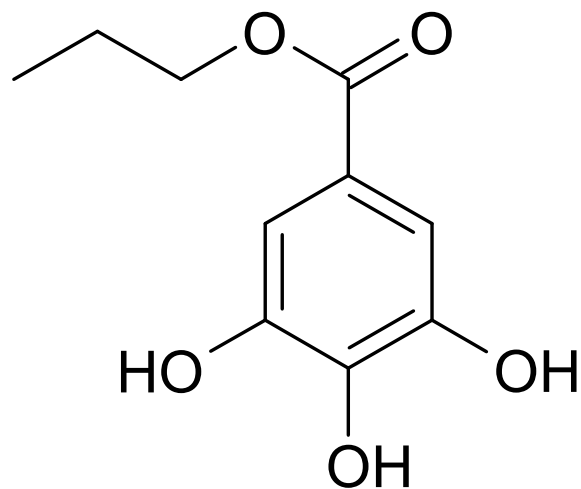
**$\gamma$ -tocopherol**  $R^1 = R^2 = \text{CH}_3$ ,  $R^3 = \text{H}$ ,  $\log P_{o/w} = 11.63$

**$\delta$ -tocopherol**  $R^1 = \text{CH}_3$ ,  $R^2 = R^3 = \text{H}$ ,  $\log P_{o/w} = 11.08$

- production: extraction of plant oils

- slowly oxidized with air  $\text{O}_2$ , quickly in presence  $\text{Fe}^{3+}$ ,  $\text{Ag}^+$

Propyl gallate

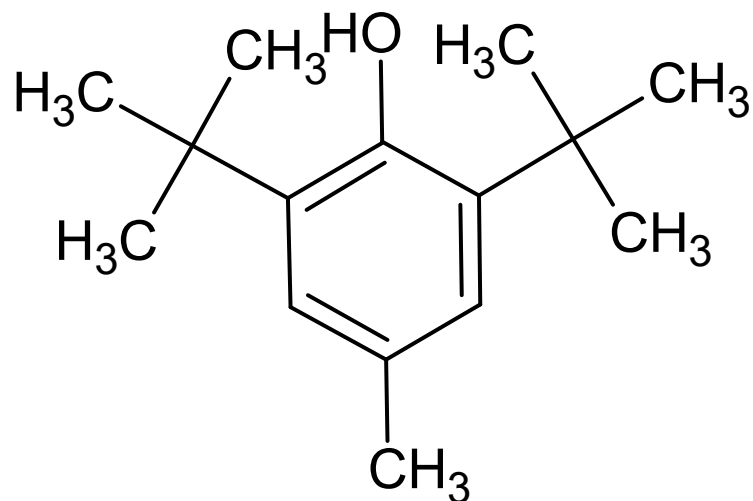
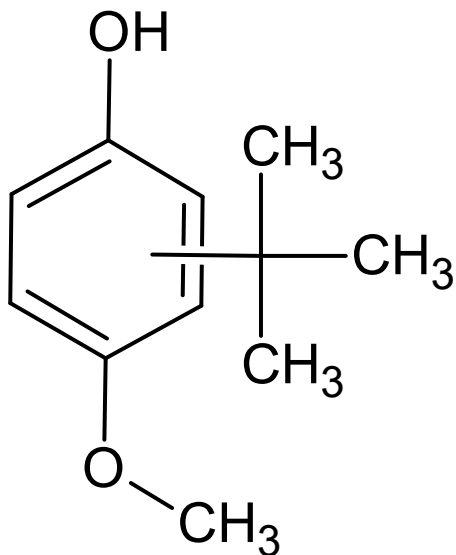


### Propyl gallate [NF]

propyl 3,4,5-trihydroxybenzoate

- antioxidant for foods, fats, oils, ethers, emulsions, waxes, and transformer oils
- preservation of lard *Adeps suilus stabilisatus PhBs 4*
- rel. hydrophilic:  $\log P_{o/w} = 1.8$  or  $0.95$ ; remains in the water phase of emulsions
- forms colored chelates with heavy metal ions

## Terc-butylated phenols



### Butylated hydroxyanisole (BHA)

[25013-16-5]

•mixture of 2- and 3-*tert*-butyl-4-methoxyphenols

PhEur + PhB: *Butylhydroxyanisolum*

BP + USPNF: Butylated hydroxyanisole

•antibact. activity

•log P<sub>o/w</sub> = 3.5

### butylhydroxytoluene (BHT)

[128-37-0]

2,6-*ditert*-butyl-4-methylphenol

PhEur + PhB: *Butylhydroxytoluenum*

BP + USPNF: Butylated hydroxytoluene

•also rubbers 0.5 – 1 %

•weak antiviral activity (*Herpes*)

•log P<sub>o/w</sub> = 5.1

•used as antioxidants in foods, cosmetics, and pharmaceuticals

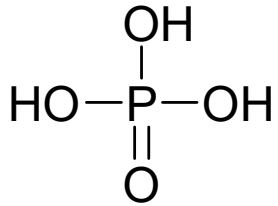
•effective concentrations:

• 0.001 – 0.02 % in oils and fats

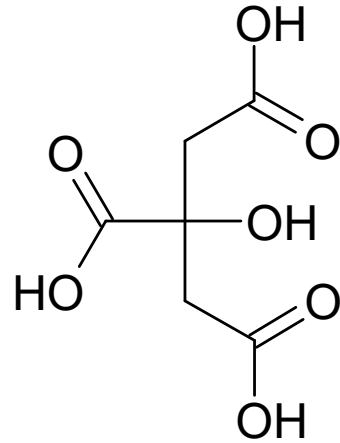
• 0.1 % in essential oils



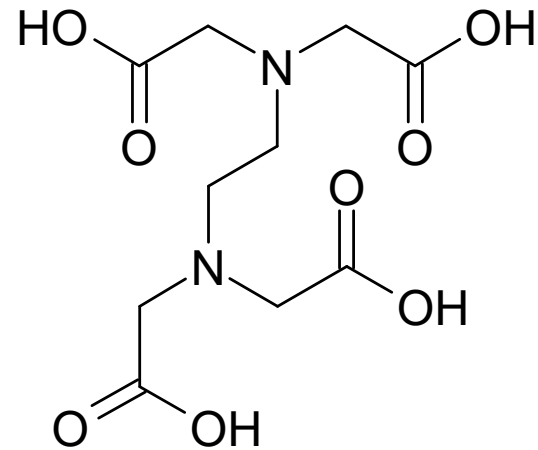
## Compounds acting synergistic with antioxidants – chelating agents



phosphoric acid



citric acid



ethylenediamine-N,N,N',N'-tetraacetic acid (EDTA)

•mostly often 2 Na<sup>+</sup> or Ca<sup>2+</sup> salt

•chelated cations are inactive as oxidation catalyzers