

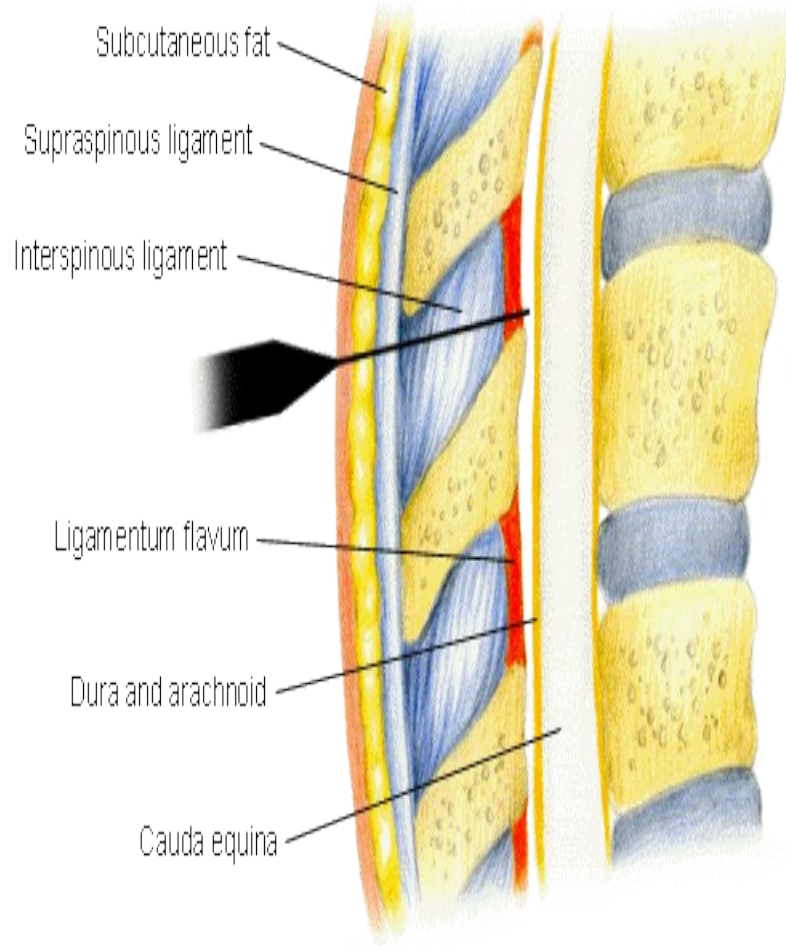
## Local anaesthetics

- drugs used for pain relief (desensitization) in site of proceeded intervention (e.g. surgical)

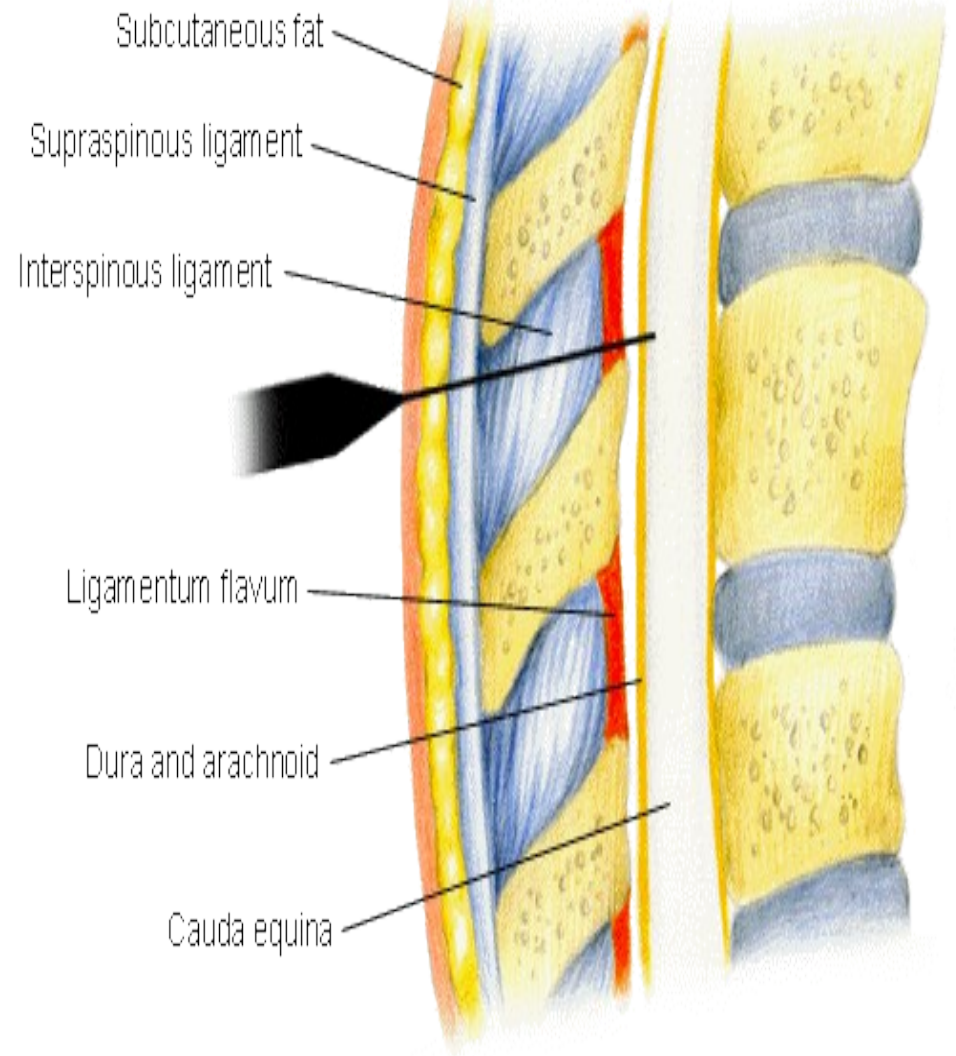
## Kinds of local anaesthesia

1. superficial – on skin and mucous membranes, borders of wounds – determined at the rabbit cornea
2. infiltration – injection to subcutaneous a submucose region – determined in guinea pigs
3. periferial nerve block – targeted to a particular nerve – determined at isolated rat *nervus ischiaticus*
4. epidural – injection at surface of *dura mater* and
5. spinal (subarachnoidal) – injection into spinal cord; both (4. and 5.) to produce anesthesia for major surgery (e.g., abdomen) or childbirth

# Epidural

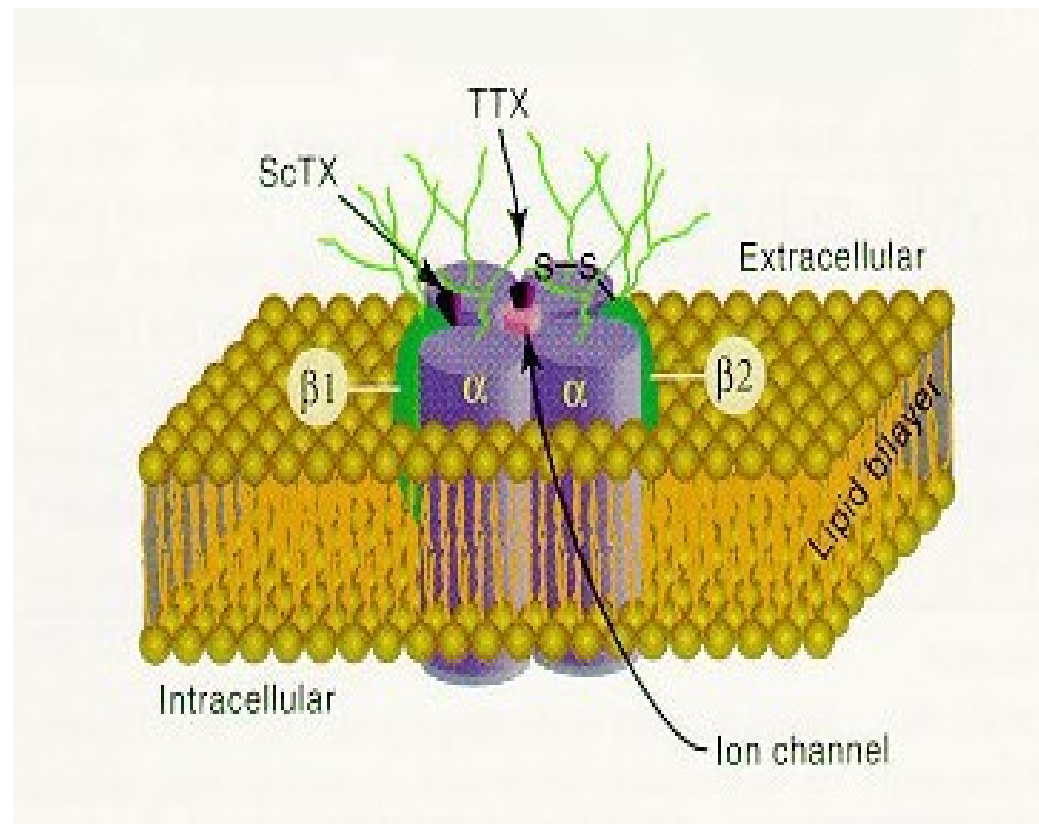


# Spinal

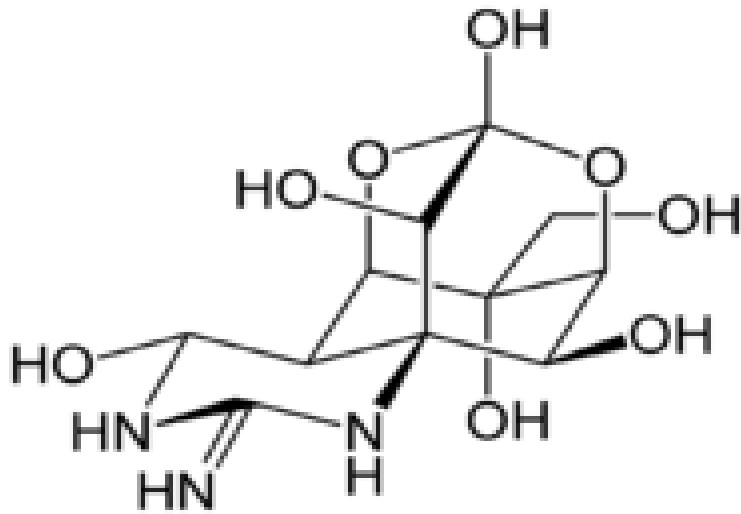


## General mechanism of action

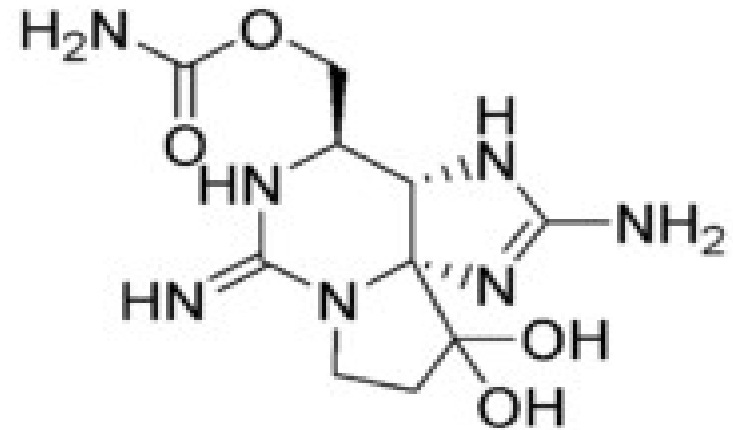
- reversibly block leading of nervous impulses through nervous axons and other cells with excitable membranes using  $\text{Na}^+$  channels for generating of action potential
- binding to receptor – sodium channel in cell membrane in its open form from the **internal (cytoplasmic) side** (In contrast, a number of highly polar toxins (e.g., tetrodotoxin TTX and saxitoxin ScTX) block the  $\text{Na}^+$  channel from the **outer surface** of the neuronal membrane)
- effect depends on pH: minimal in acidic media (weak bases dissociated in acidic media, poor permeation into  $\text{Na}^+$  channels)  $\Rightarrow$  poorly active in a tissue where is inflammation
- increased extracellular  $\text{Ca}^{2+}$  concentration antagonizes their effect due to increase of superficial potential on a membrane



Polar toxins blocking the Na<sup>+</sup> channel from the outer surface of the neuronal membrane



**tetrodotoxin** (puffer fish; several genera of *Tetraodontidae* family)  
•log P = -6.210

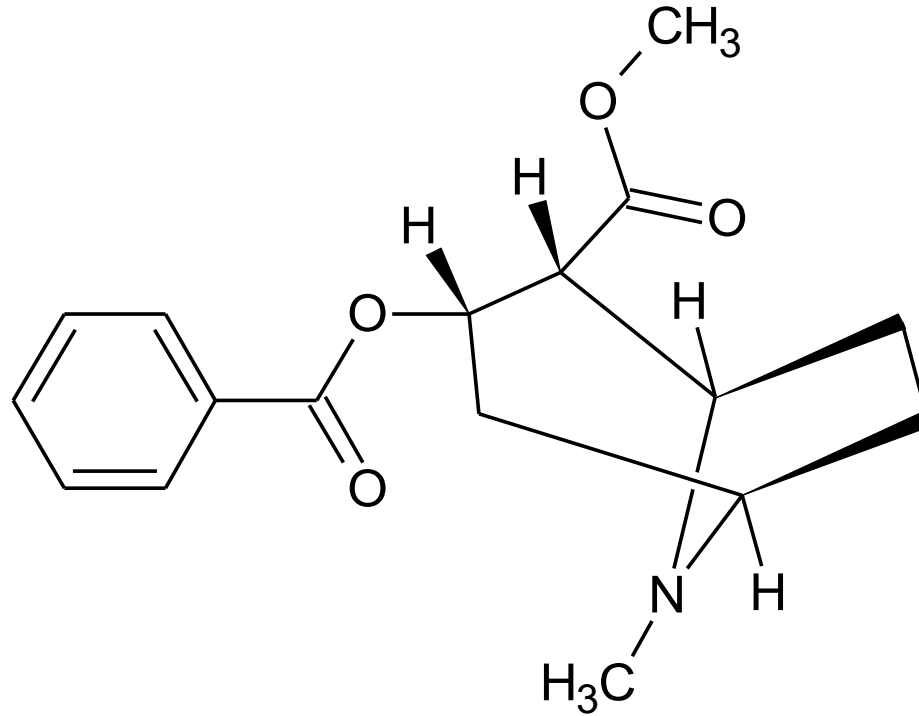


**saxitoxin** (shell fish; edible moluscs of various genera; the toxin itself is produced by planctonic protozoa *Gonyaulax catenella* and consumed by moluscs)

## Unwanted effects - toxicity

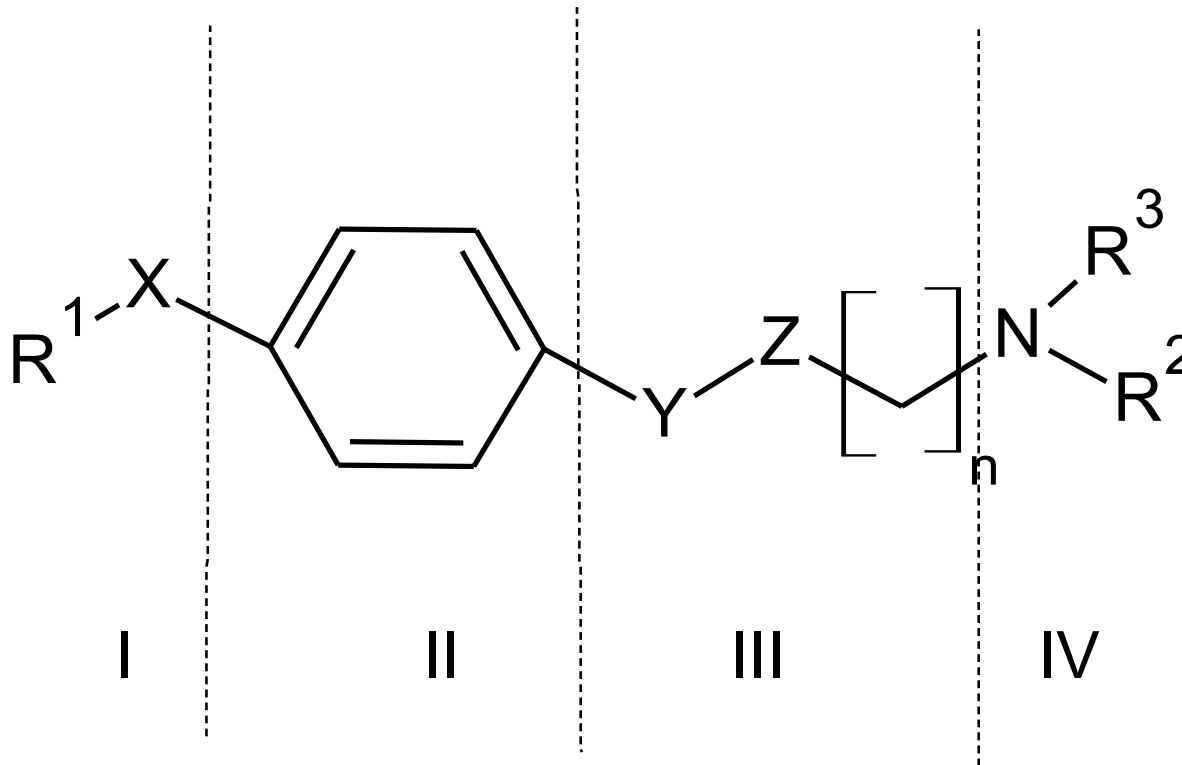
- generally smaller in less stable esters
- CNS: sleepiness, photodysphoria, failures of vision and hearing, convulsions; early symptoms: insensitivity of tongue, metallic taste
- peripheral NS: temporary neuropathies
- ♥and vessels: decrease of contraction strength, ECG changes, dilation of arteriols, decrease or reflection increase of pressure
- alergies: esters (4-aminobenzoic acid is alergene)

Cocaine – prototype = „lead compound“ of local anaesthetics



- contained in leaves of coca shrub *Erythroxylon coca*, isolated by Niemann 1860, Koller begun its clinical usage 1884 in ophthalmology, structure elucidated by Willstätter (1898) including total synthesis
- additional 30 years the only one local anaesthetic
- centrally-stimulating effects, strongly addictive; today again only in ophthalmology
- comparative standard for evaluation of activity of (novel) local anaesthetics
- the suffix **-caine** of INN names of all local anaesthetics originated from cocaine

General structure of local anaesthetics – SAR (structure-activity relationships) = common „building principle“ of local anaesthetics



Region I: electron-donor substituent

Region II: lipophilic aromatic ring

Region III: linking chain

Region IV: basic substituent – tertiary amino group

R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>: alkyls (R<sup>2</sup>+R<sup>3</sup> can be connected a saturated ring)

X: typically NH

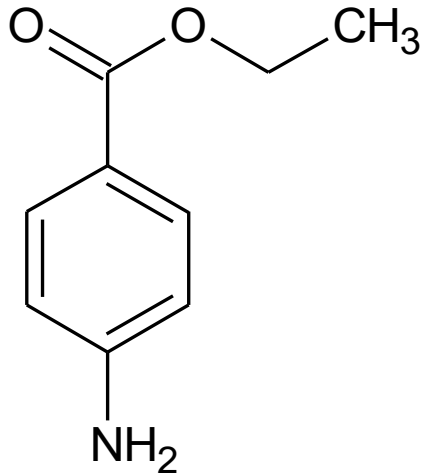
Y-Z: COO, CONH, NHCO, NHCOO



## Classification of local anaesthetics according to their structures

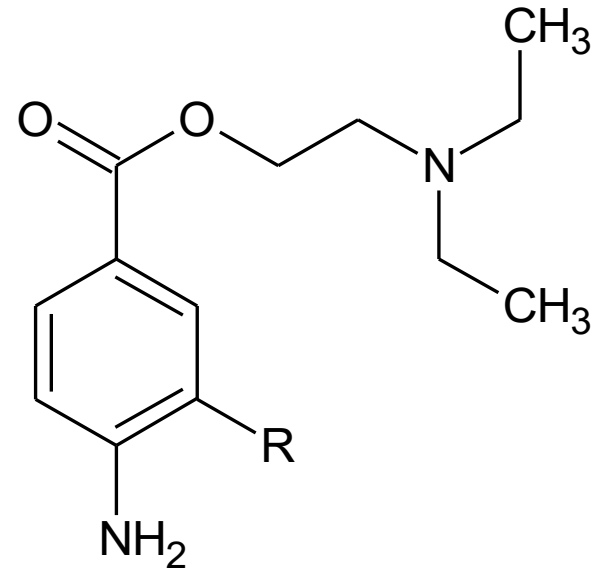
1. Esters
2. Amides
3. Anilides
4. Carbamates

## 1. 4-aminobenzoic acids esters



**benzocaine**

- the simplest
- very weakly basic  $\Rightarrow$  used as free base
- stomatology
- Benzocainum* PhEur



**R = H    procaine**

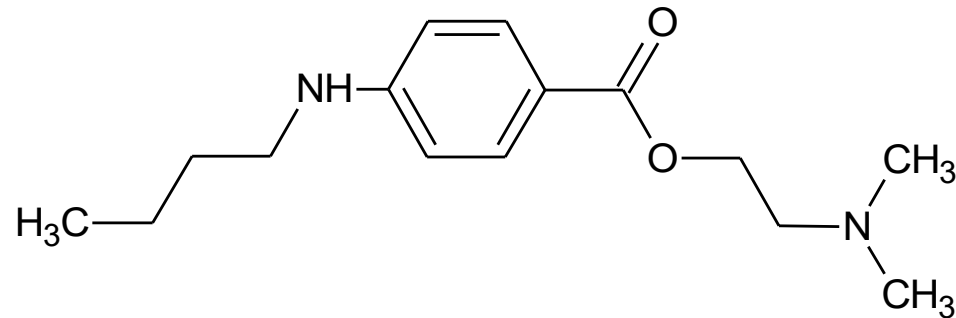
- Alfred Einhorn 1905
- hydrochloride
- poorly soluble salt with benzylpenicilline for depot *i.m.* administration
- Procaini hydrochloridum* PhEur

**R = OC<sub>4</sub>H<sub>9</sub>    oxybuprocaine**

- Oxybuprocaini hydrochloridum* PhEur

- lower effect of antibacterial sulfonamides (resources of 4-aminobenzoic acid)

## 1. 4-aminobenzoic acids esters

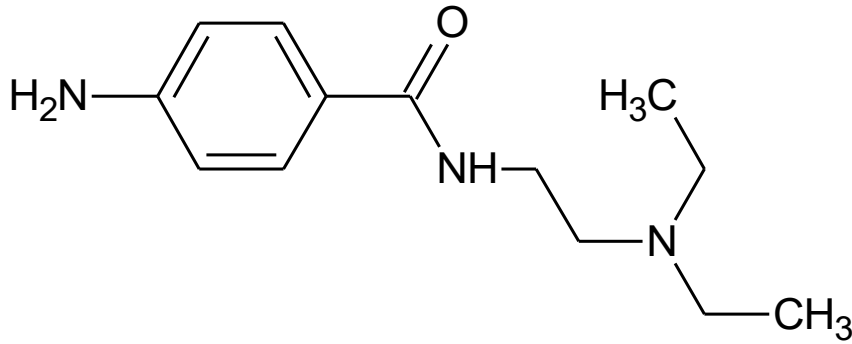


### **tetracaine**

- topical, infiltration and spinal anaesthesia
- topically in ophthalmology
- slow onset of action and its longer lasting than in procaine (the longest among esters)
- about 10x more toxic and effective than procaine

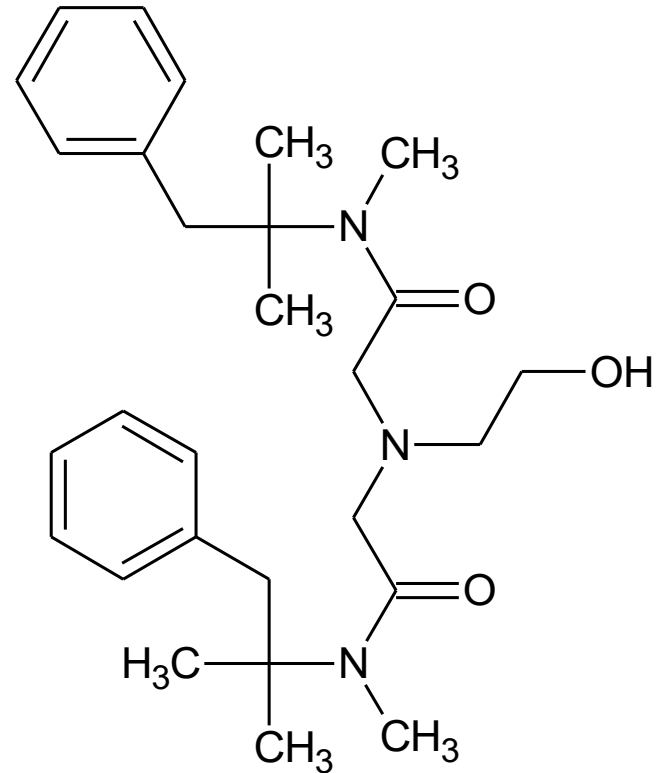
## 2. Amides

- mnemotechnic rule of pronounced „i“ - includes also anilides



### procainamide

- amide isosteric analogue of procaine
- also antidysrhythmic effects: the amide bond is more stable than the ester one thus it can be delivered into heart in satisfactory concentration
- Procainamidi hydrochloridum* PhEur



### oxethacaine [INN] syn. oxethazaine [USAN: BAN: JAN]

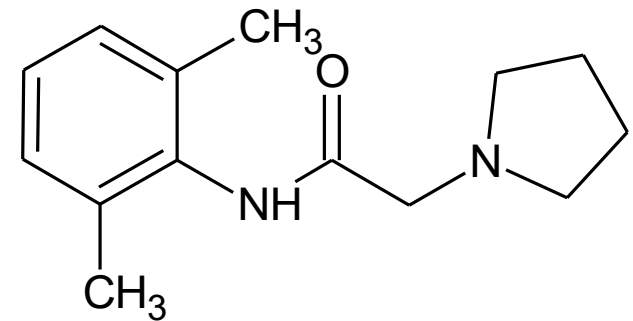
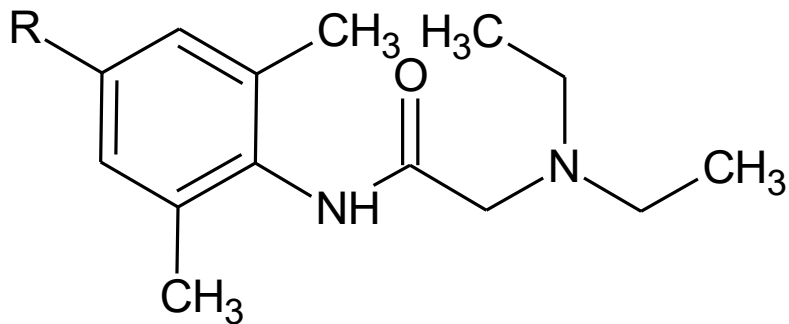
2,2'-[(2-hydroxyethyl)imino]bis[N-(1-phenyl-2-methyl-2-propyl)-N-methylacetamide]

- usage with antacids: Anacid compositum<sup>®</sup>

### 3. Anilides

- also amides; in contrast to previous group isosteric change performed: „reversion“ of the amide bond  $\Rightarrow$  N-phenyl amino acid amides

Acetanilides with a basic substituent



**pyrrocaine**

R = H **lidocaine**

- prepared by Nils Löfgren 1943
- most frequently used; all ways of administration
- Lidocaini hydrochloridum monohydricum* PhEur
- forms various hydrates
- Xylocaine<sup>®</sup>

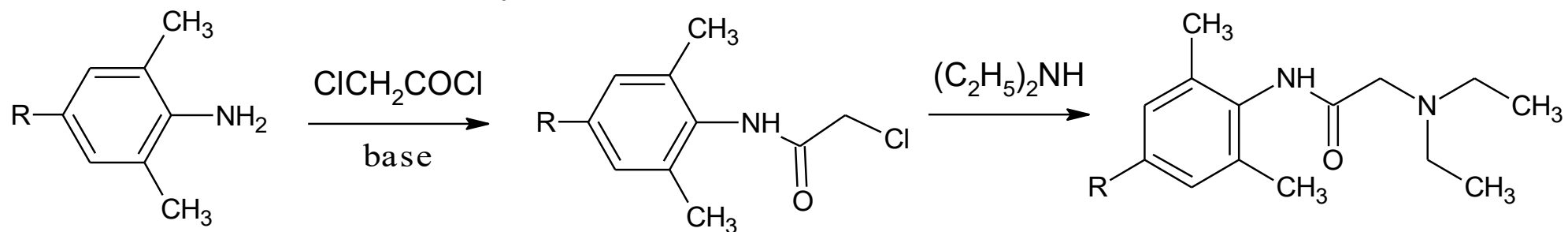
R = CH<sub>3</sub> **trimecaine**

- Mesocaine<sup>®</sup>

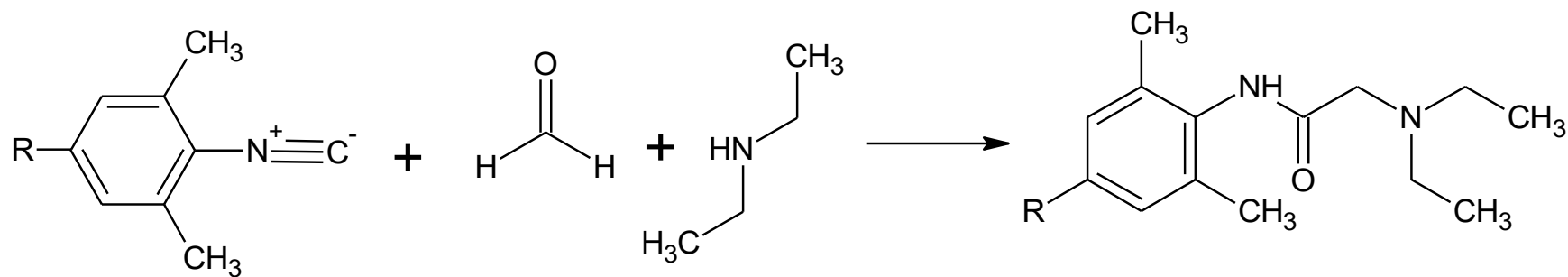
- also antidysrhythmics

## Syntheses of lidocaine a trimecaine

"Classical" - also in practical classes in MC

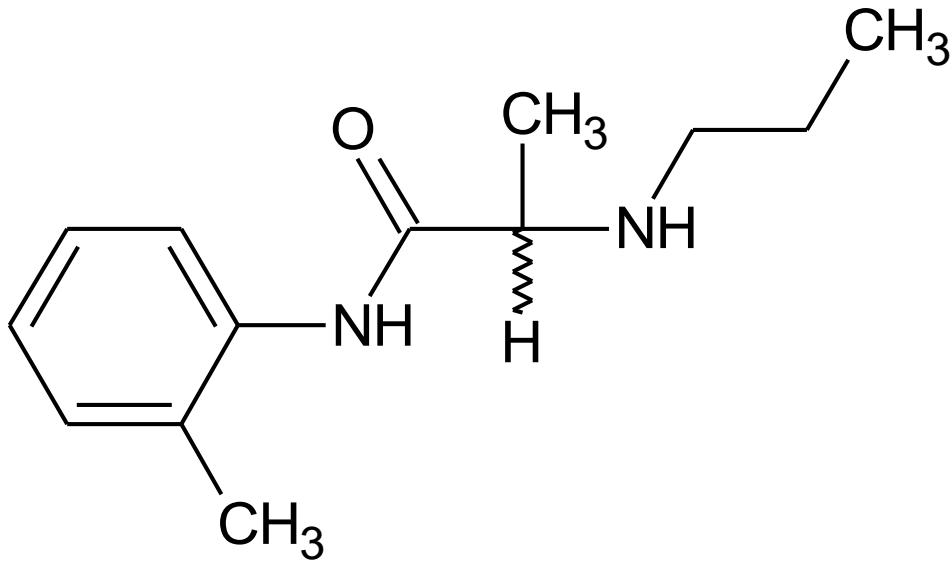


Ugi condensation



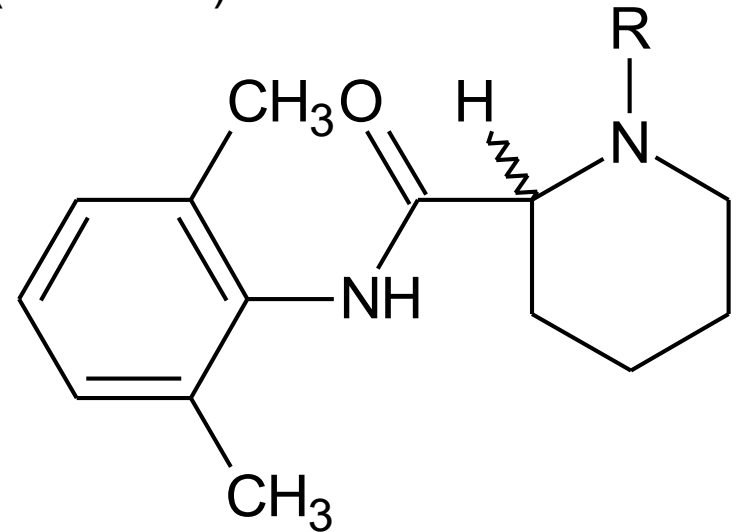
$\text{R} = \text{H}$  or  $\text{CH}_3$

## Anilides (continued)



### prilocaine

- fastest hydrolyzed compound in group of anilides
- Prilocaini hydrochloridum* PhEur
- AE: methemoglobinemia (o-toluidine:  $Fe^{II} \rightarrow Fe^{III}$ )



R =  $CH_3$       **mepivacaine**

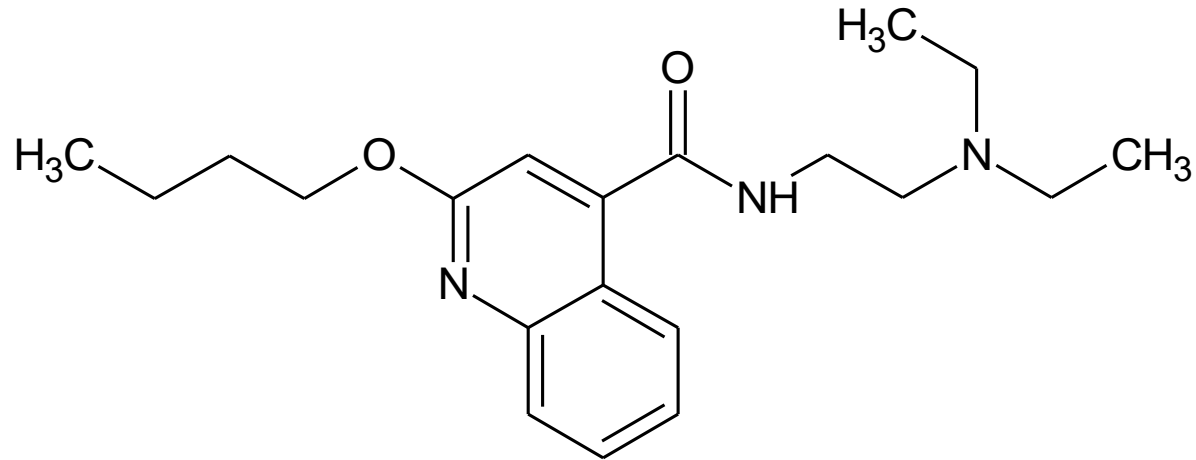
R =  $C_3H_7$       **ropivacaine**

- nearly ideal local anaesthetics:
- fast onset of action
- long lasting
- selective block of sensoric nerves without motoric block
- minimal local irritability and no systemic toxicity

R =  $C_4H_9$       **bupivacaine**

- slowest hydrolyzed
- cardiotoxicity
- (-)-enantiomer = **levobupivacaine** less cardiotoxic but also less efficient and with shorter time of activity
- used in obstetrics

## Anilides (continued)



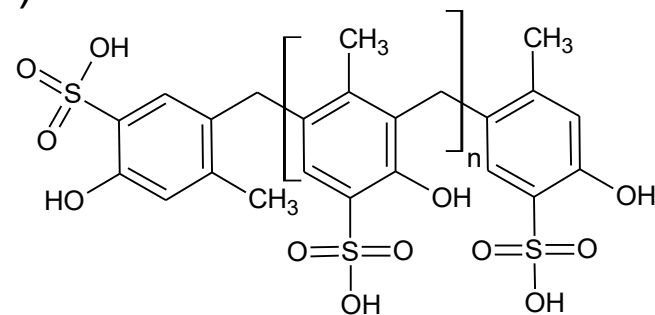
### **cinchocaine**

dibucaine [USP]

•Meischer 1925

•inhibits pseudocholinesterase; used to detect abnormality of this enzyme

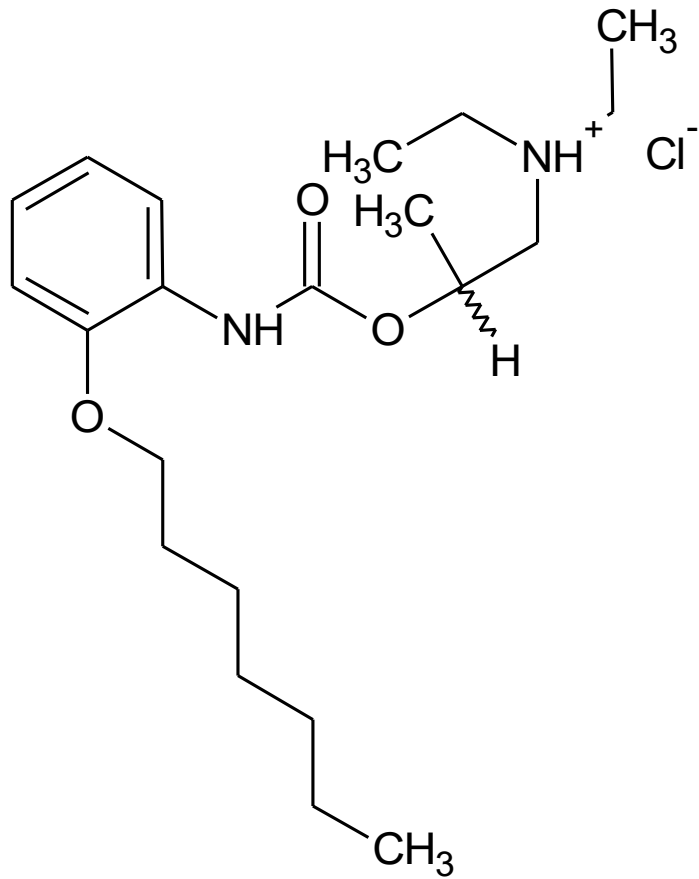
Faktu ® sup., ung. (+ polycresulene) for treatment of hemorrhoids



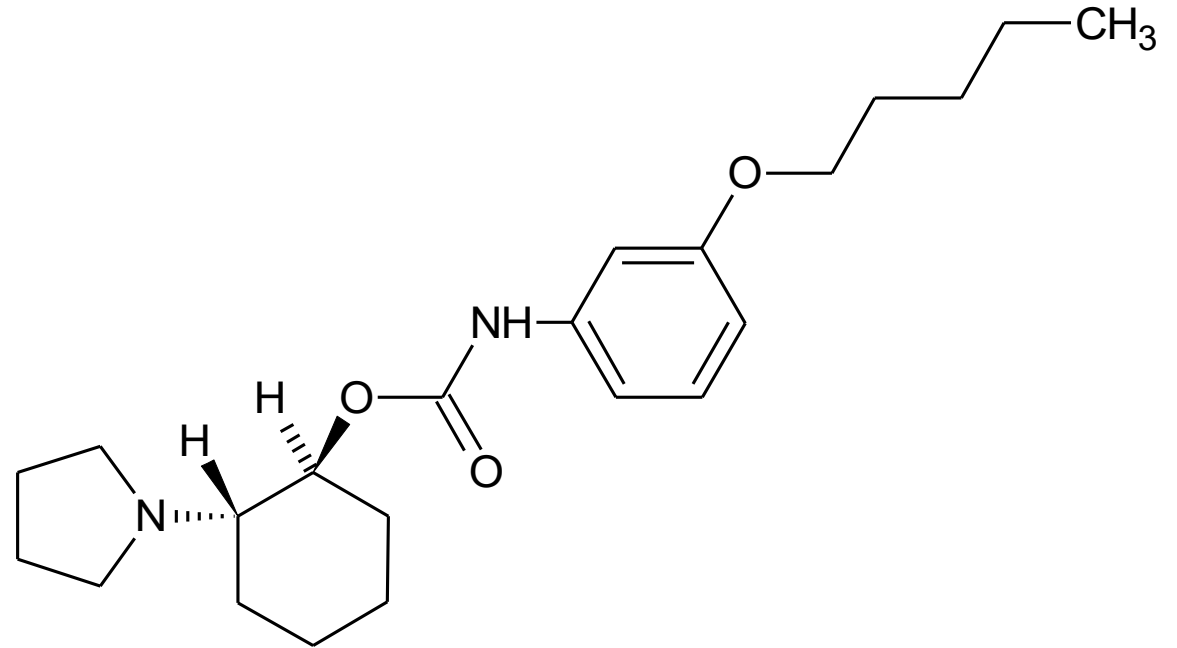
polycresulene



## 4. Carbamates



**carbisocaine**



**trapencaine**

syn. pentacaine

•also anti-ulcer effect