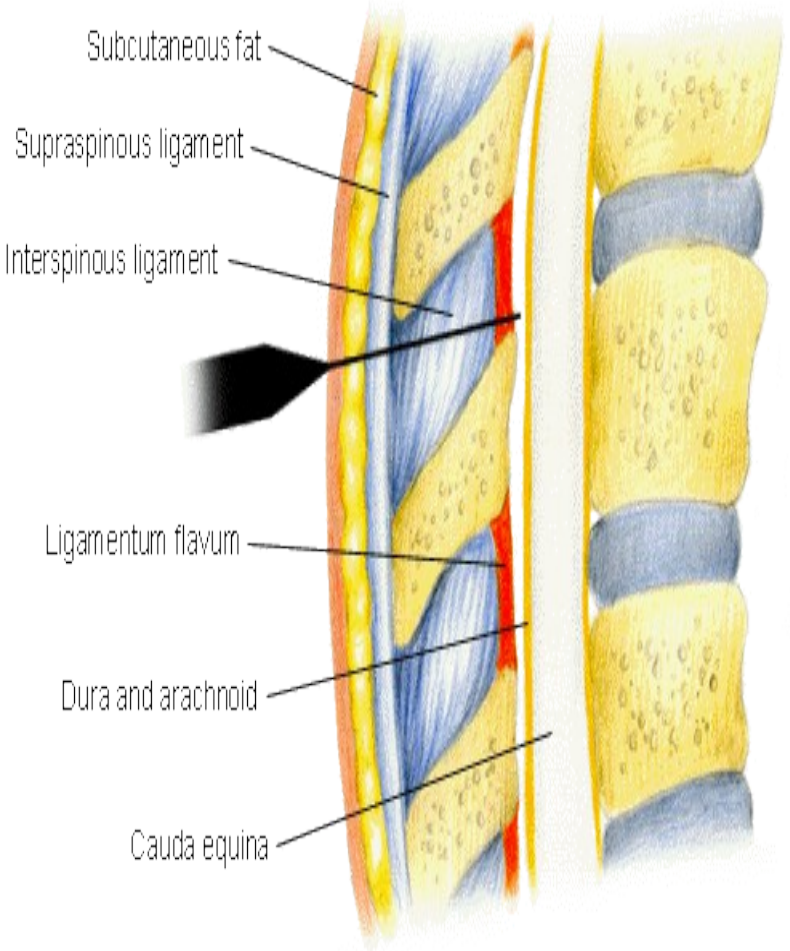
Local anaesthetics

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

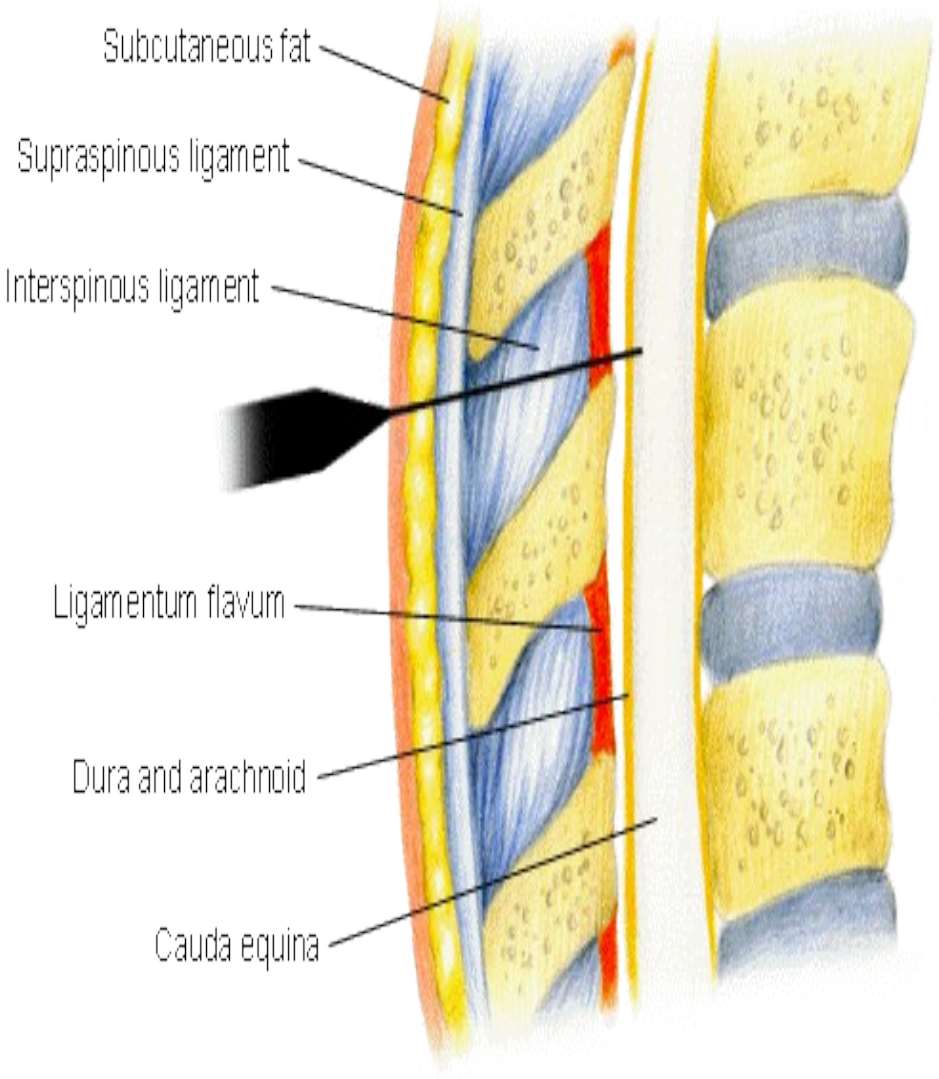
Kinds of local anaesthesia

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



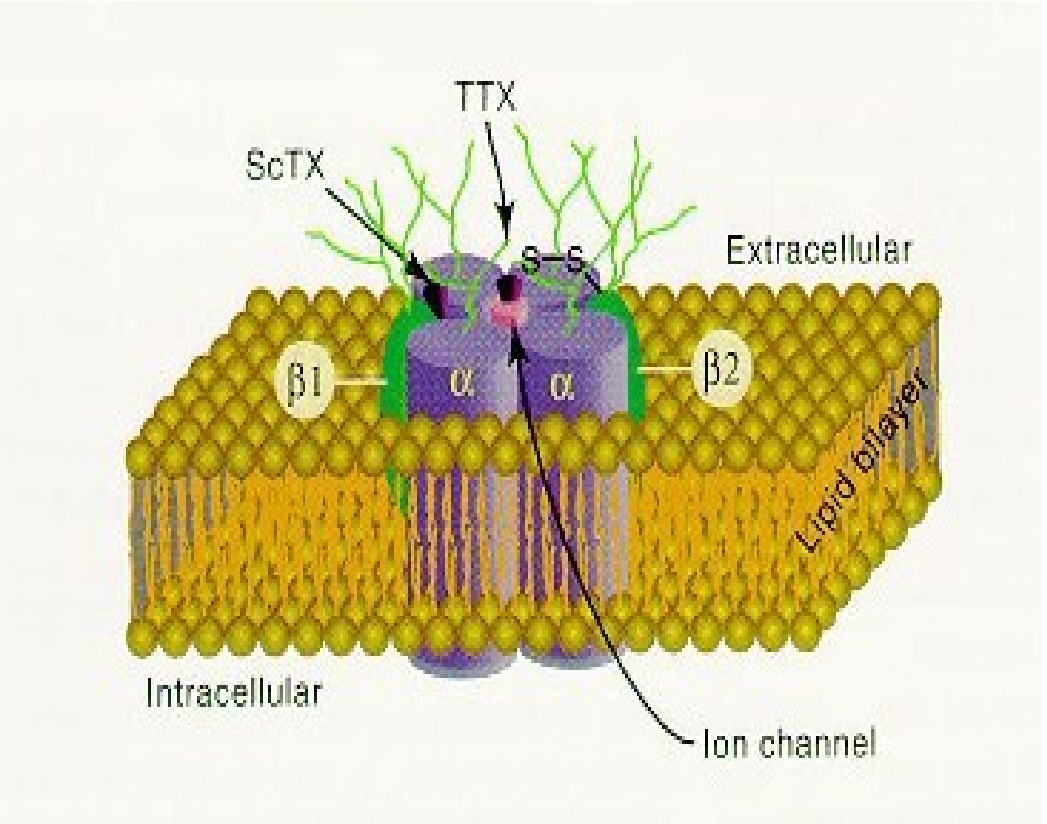
General mechanism of action

•reversibly block leading of nervous impulses through nervous axons and other cells with excitable membranes using Na^+ channels for generating of action potential

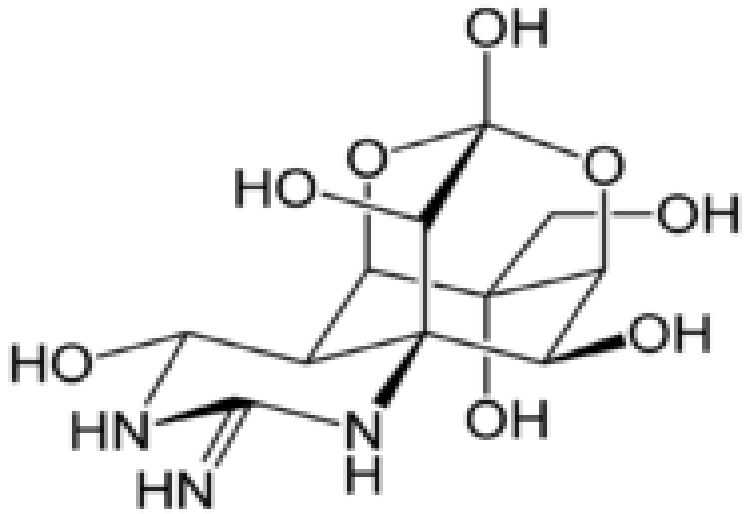
•binding to receptor – sodium channel in cell membrane in its open form from the internal (cytoplasmic) side (In contrast, a number of highly polar toxins (e.g., tetrodotoxin TTX and saxitoxin ScTX) block the Na^+ channel from the outer surface of the neuronal membrane)

•effect depends on pH: minimal in acidic media (weak bases dissociated in acidic media, poor permeation into Na^+ channels) $\Rightarrow$ poorly active in a tissue where is inflammation

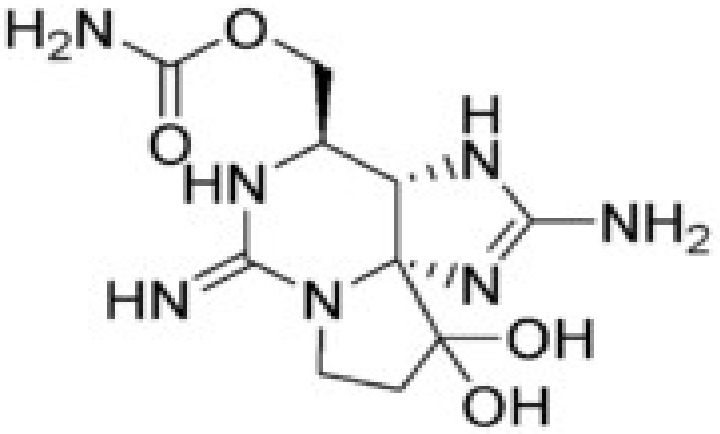
•increased extracellular Ca^{2+} concentration antagonizes their effect due to increase of superficial potential on a membrane



Polar toxins blocking the Na^+ channel from the outer surface of the neuronal membrane



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

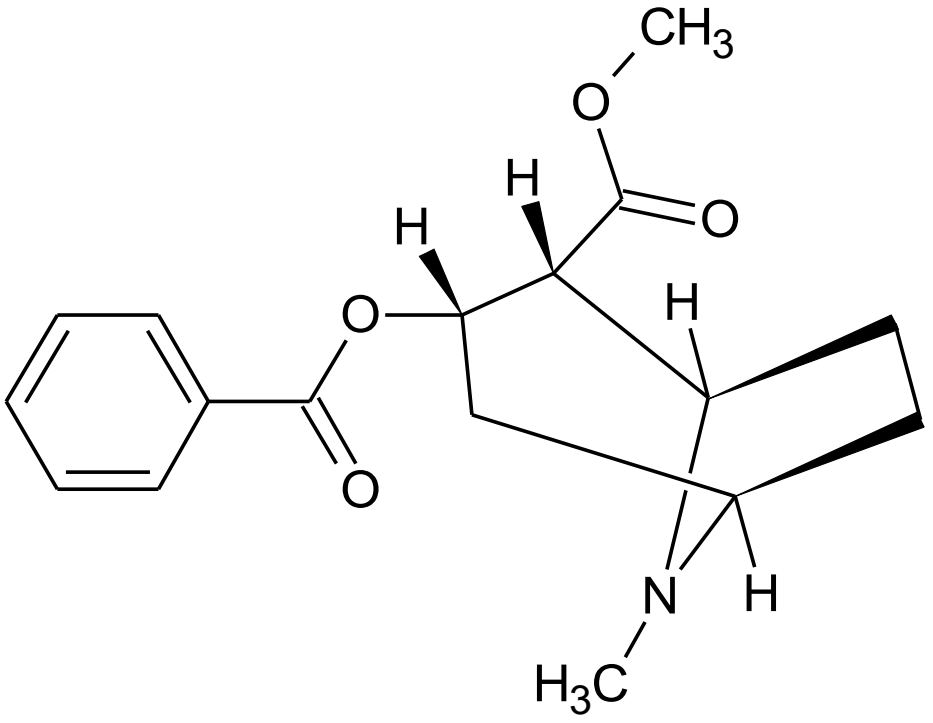


saxitoxin (shell fish; edible moluscs of various genera; the toxin itself is produced by planctonic protozoa *Gonyaulax catenella* and consumed by moluscs)

Unwanted effects - toxicity

- generally smaller in less stable esters
- CNS: sleepiness, photodysphoria, failures of vision and hearing, convulsions; early symptoms: insensitivity of tongue, metalic taste
- peripherial NS: temporary neuropathies
- ♥and vessels: decrease of contraction strenghth, 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 ophtalmology, structure elucidated by Willstätter (1898) including total synthesis

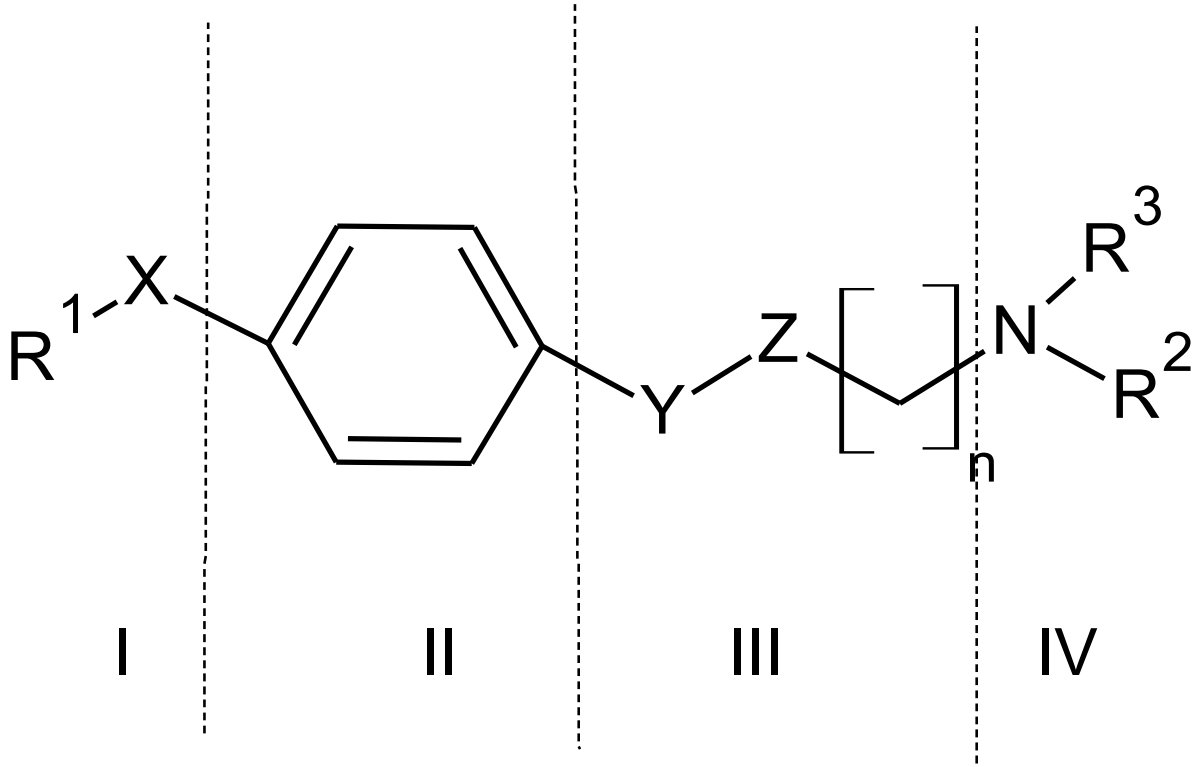
•additional 30 years the only one local anaesthetic

•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 anaethetics – 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^1,R^2,R^3: alkyls (R^2+R^3 can be connected a saturated ring)

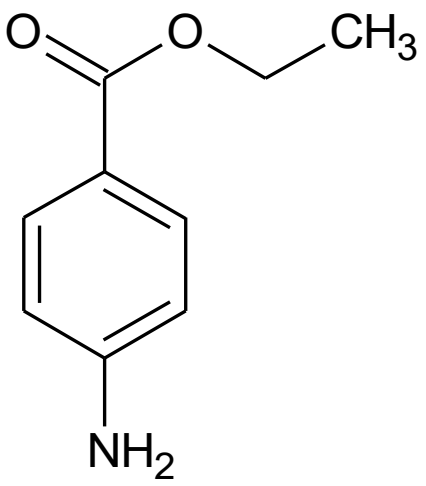
X: typically NH

Y-Z: COO, CONH, NHCO, NHCOO

Classification of local anaesthetics according to their structures

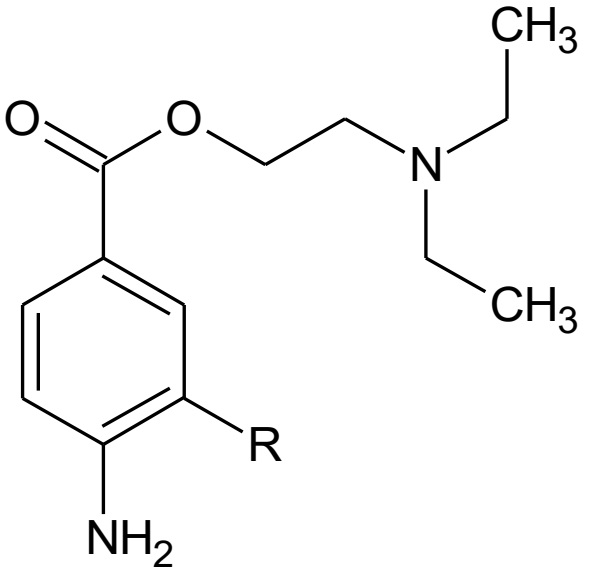
1. Esters
2. Amides
3. Anilides
4. Carbamates

1. 4-aminobenzoic acids esters



benzocaine

- the simpliest
- very weakly basic ⇒ used as free base
- stomatology
- *Benzocainum* PhEur



R = H procaine

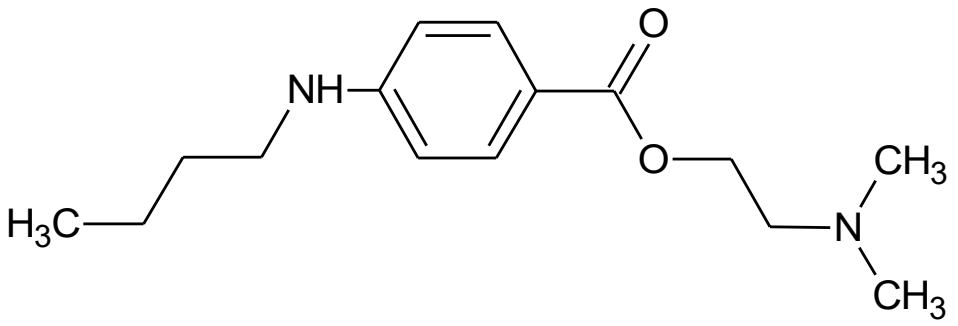
- Alfred Einhorn 1905
- hydrochloride
- poorly soluble salt with benzylpenicilline for depot *i.m.* administration
- *Procaini hydrochloridum* PhEur

R = OC_4H_9 oxybuprocaine

- *Oxybuprocaini hydrochloridum* PhEur

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

1. 4-aminobenzoic acids esters

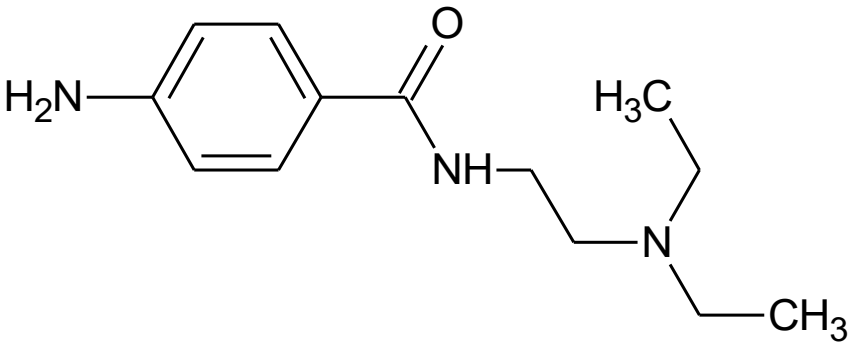


tetracaine

- 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

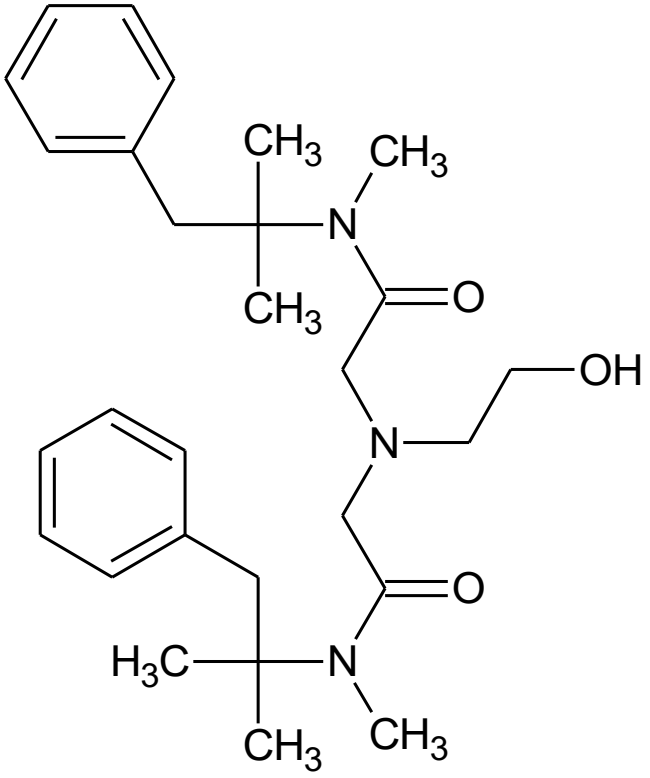


procainamide

•amide isosteric analogue of procaine

•also antidysrythmic effects: the amide bond in more stable than the ester one thus it can be delivered into heart in satisfactory concentration

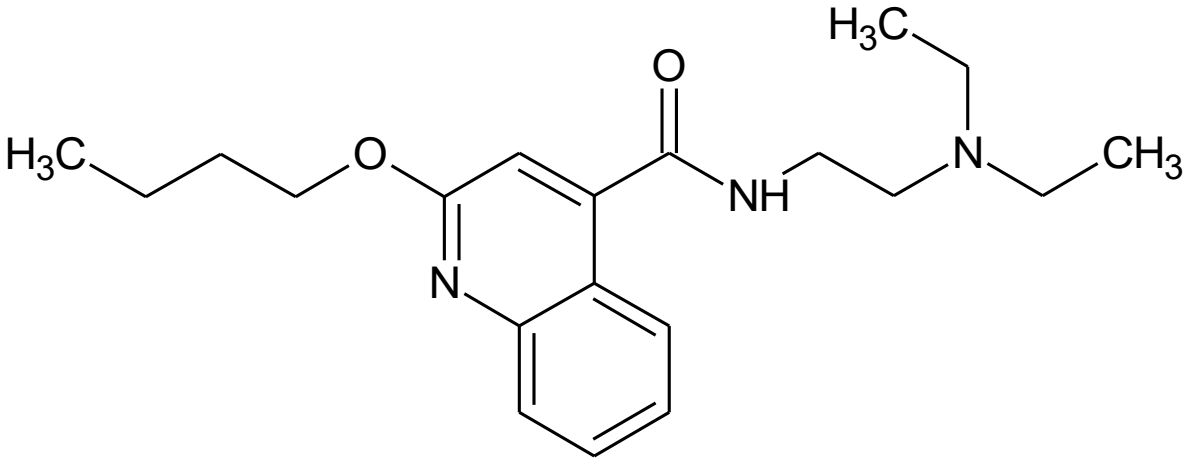
•*Procainamidi hydrochloridum* PhEur



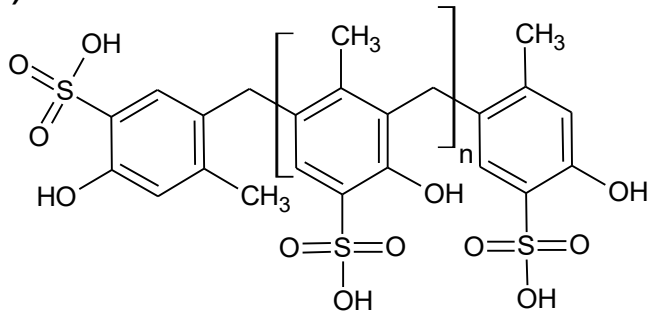
oxethacaine [INN] syn. oxethazaine [USAN:BAN:JAN]

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

•usage with antacids: Anacid compositum®



cinchocaine
dibucaine [USP]
•Meischer 1925
•inhibits pseudocholinesterase; used to detect abnormality of this enzyme
Faktu ® sup., ung. (+ policresulene) for treatment of hemorrhoids

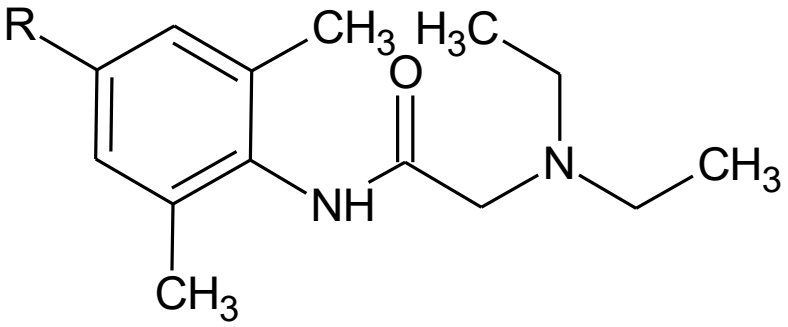


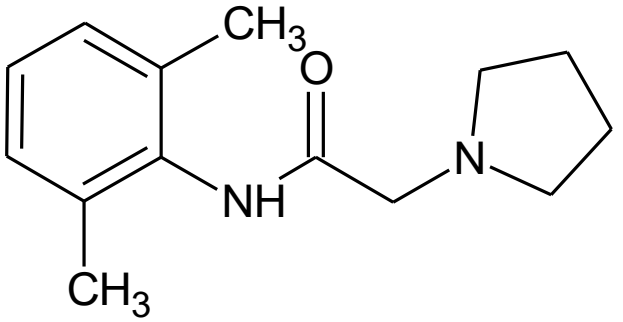
policresulene

3. Anilides

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

Acetanilides with a basic substituent





pyrrocaine

R = H **lidocaine**

•prepared by Nils Lögfren 1943

•most frequently used; all ways of administration

•*Lidocaini hydrochloridum monohydricum* PhEur

•forms various hydrates

•Xylocaine®

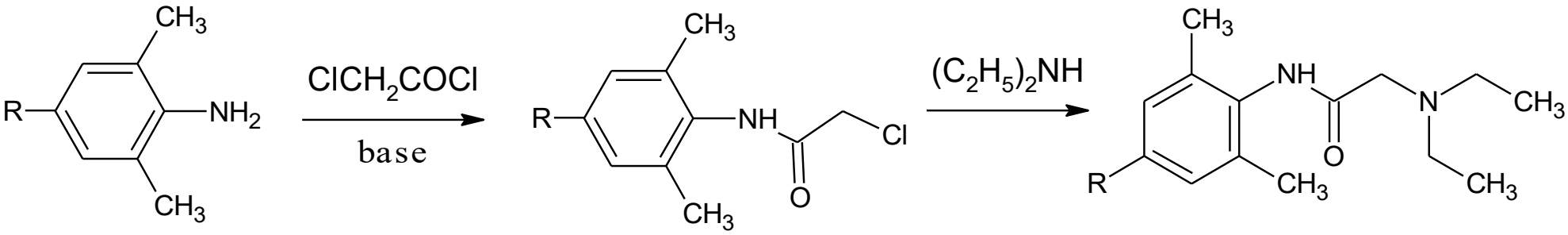
R = CH_3 **trimecaine**

•Mesocaine®

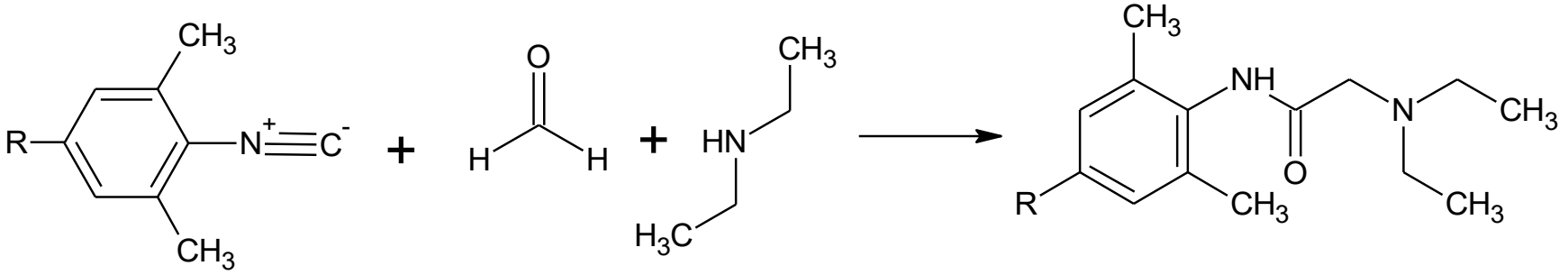
•also antidysrythmics

Syntheses of lidocaine a trimecaine

"Classical" - also in practical classes in MC

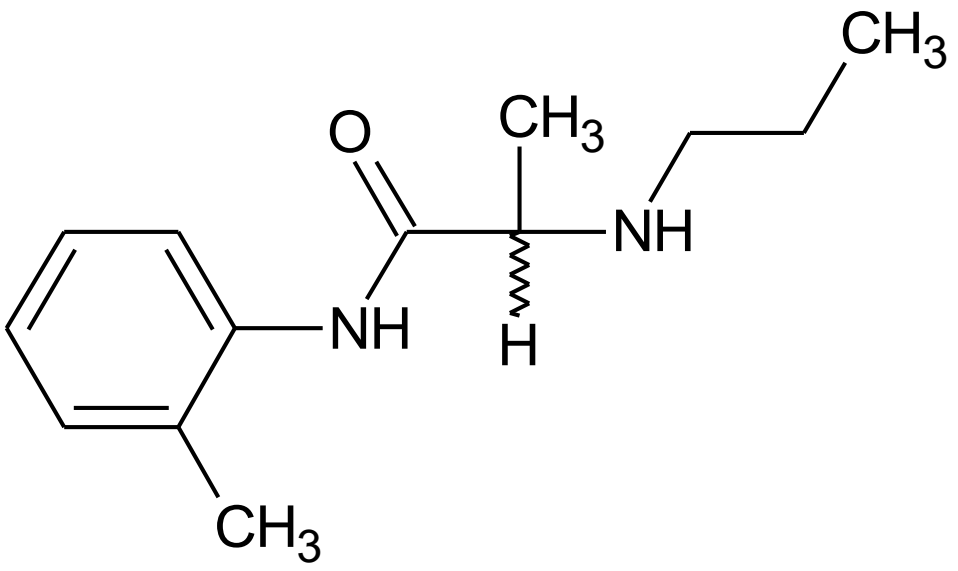


Ugi condensation



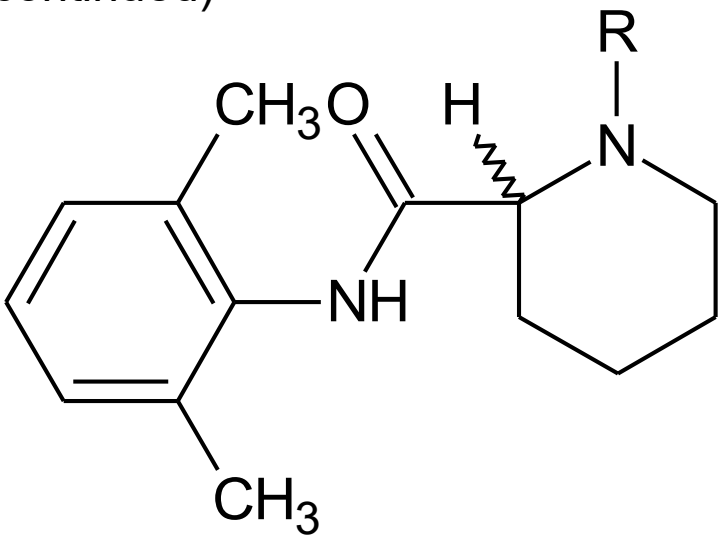
R = H or CH_3

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**

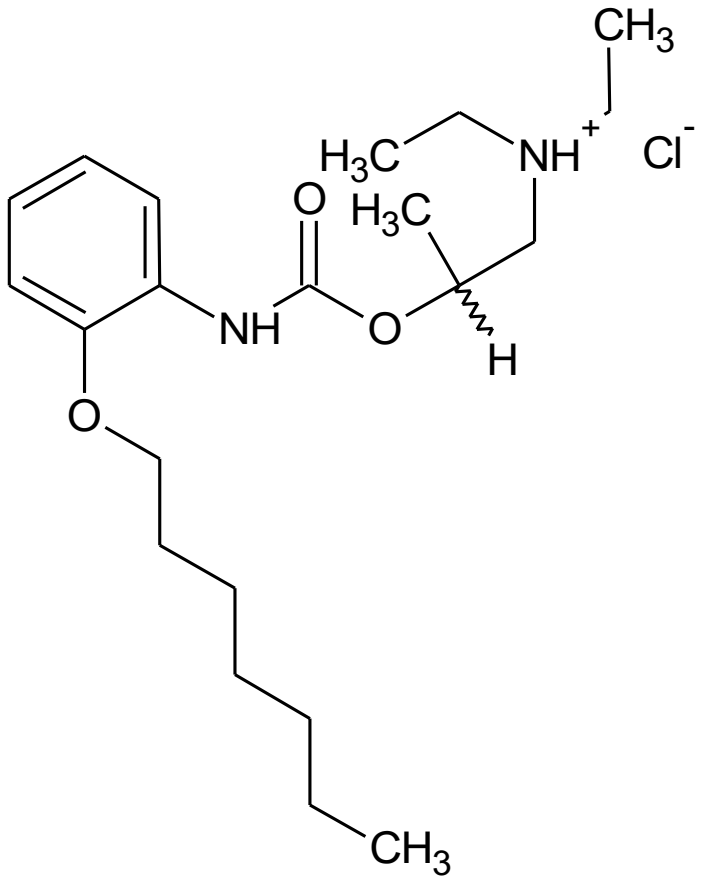
R = C_3H_7 **ropivacaine**

- 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

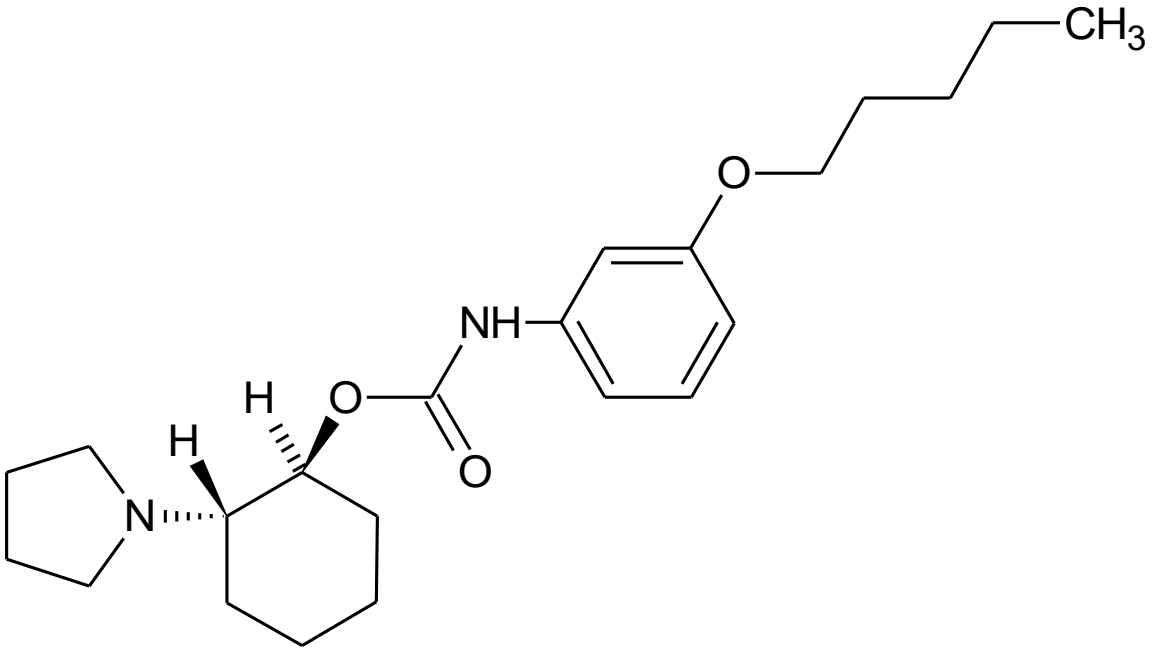
R = C_4H_9 **bupivacaine**

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

4. Carbamates



carbisocaine



trapencaine
syn. pentacaine
•also anti-ulcer effect