

# Local Anesthetics

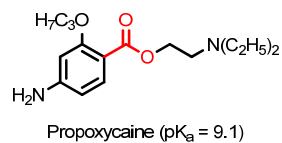
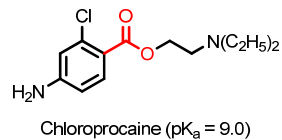
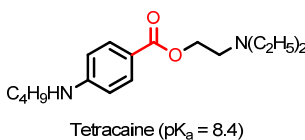
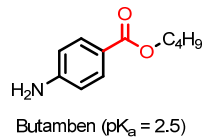
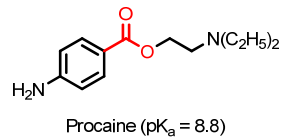
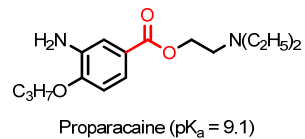
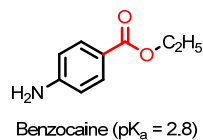
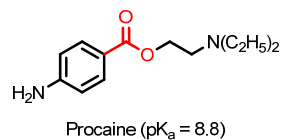
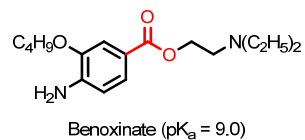
- Anesthesia is the loss of sensation with or without loss of consciousness.

- Drugs with diverse chemical structures are anesthetics:

- ✓ Local anesthetics.
- ✓ General anesthetics.
- ✓ CNS depressants:
  - Analgesics.
  - Barbiturates.
  - Benzodiazepines.
  - Anticonvulsants.
  - Muscle relaxants.

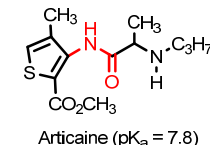
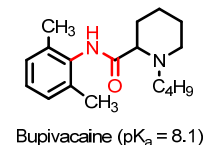
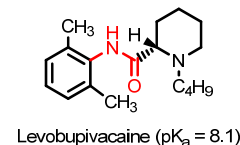
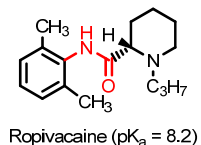
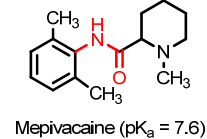
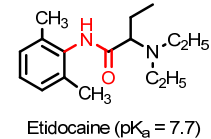
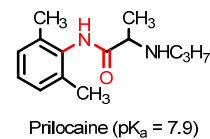
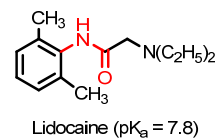
## Local Anesthetics

- Local anesthesia.
- Without loss of consciousness.
- Topically or parenterally.
- Interfere with Na channels (**action potential**).
- Decrease excitability of nerve membranes.
- Block nerve conductance in both sensory and motor neurons.



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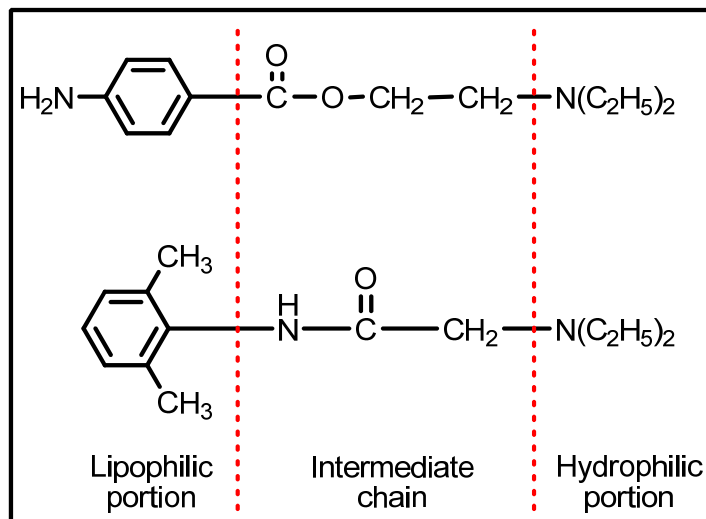
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6

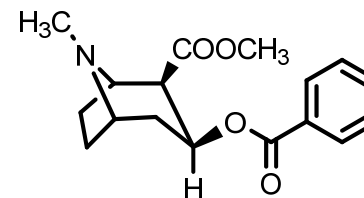
## Chemical Structures of Local Anesthetics



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7

## Discovery



Cocaine

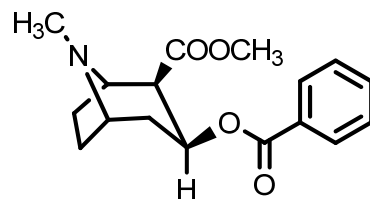
- Saliva from chewing the coca leaves (1532).
- Relieve painful wounds.
- First isolated in 1860.
- First used as a local anesthetic in 1884.
- Lead compound.

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8

## Was (is) Cocaine an Ideal Drug?

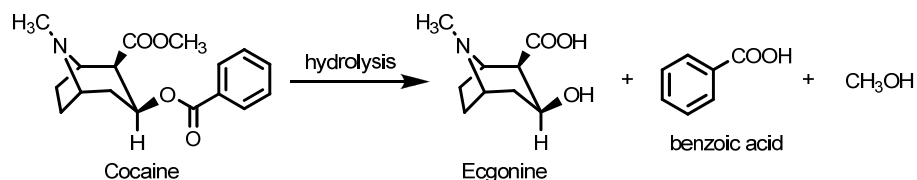
- Major drawback:
  - ✓ **Psychic dependence.**
- Other drawbacks:
  - ✓ **Allergic reactions.**
  - ✓ **Tissue irritations.**
  - ✓ **Poor stability in aqueous solution.**



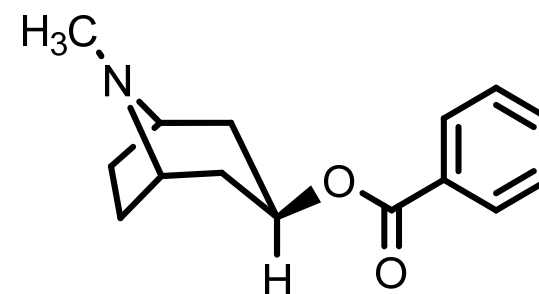
Cocaine

## Development

- Two Strategies:
  - ✓ Search for new active compounds (**Chance**).
  - ✓ Modify compounds in hand (**Structure???**).

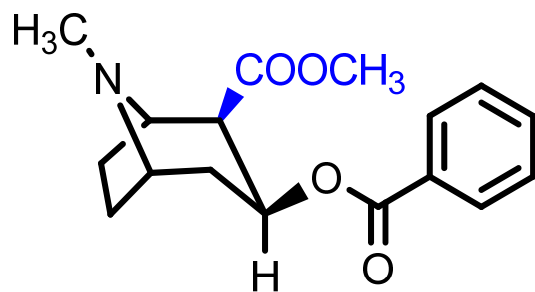


- Structure of cocaine was not known until 1924.
- The structures of the hydrolysis products were elucidated.



Benzoylatropine

- Strong local anesthetic properties.
- **No addicting liability.**

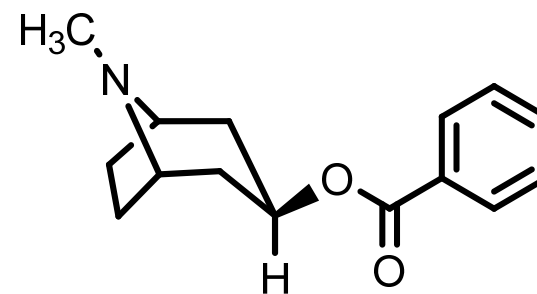


Cocaine

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13

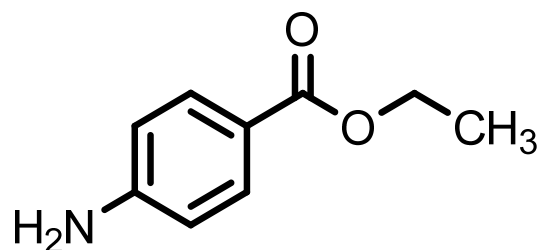


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14

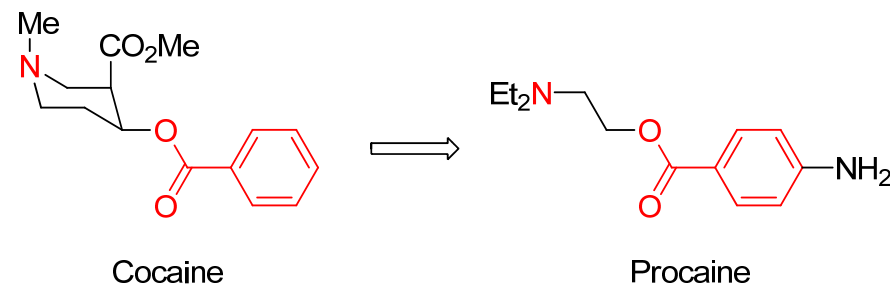
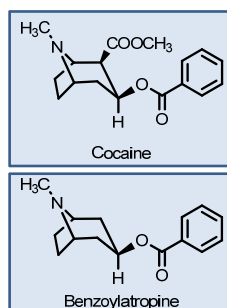


Benzocaine ( $pK_a = 2.8$ )

- 1890.
- Good anesthetizing properties and low toxicity.
- Poor water solubility (no hydrophilic portion).
- No parenteral solutions.

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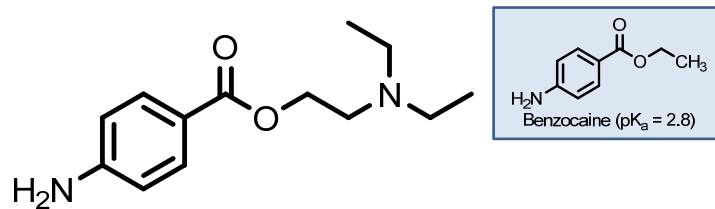
15



- Simplification of cocaine.
- Pharmacophore, shown in red color, consists of:
  - An amine.
  - An ester.
  - An aromatic ring.

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16

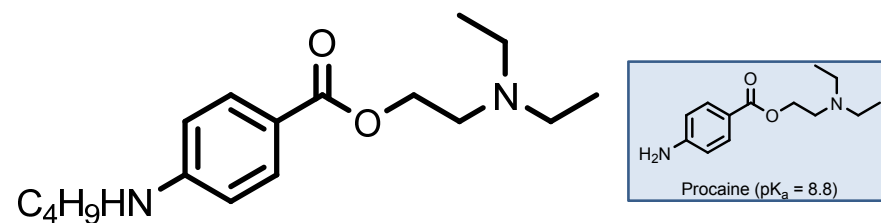


Procaine ( $pK_a = 8.8$ )

- Prototype (1905).
- Less toxic than cocaine.
- Water soluble (HCl salt).
- Short duration of action (hydrolysis).
- Combination with epinephrine.

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17

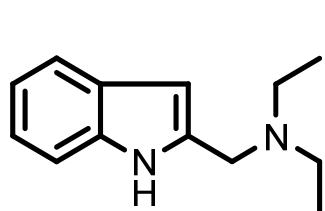


Tetracaine ( $pK_a = 8.4$ )

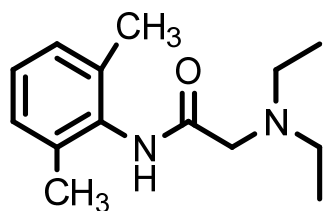
- Most potent, long-acting ester-type.
- Used in spinal anesthesia.

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18



isogramine

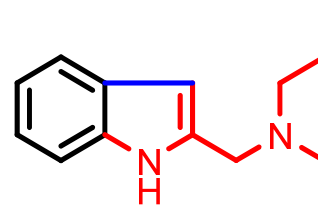


Lidocaine ( $pK_a = 7.8$ )

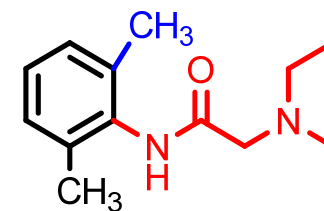
- Natural alkaloid.
- Serendipitous discovery of LA (1935).
- Led to the discovery of lidocaine (Xylocaine).

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19



isogramine

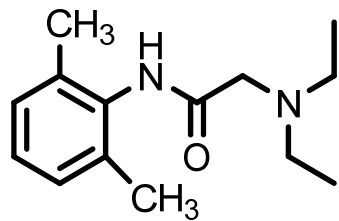


Lidocaine ( $pK_a = 7.8$ )

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20

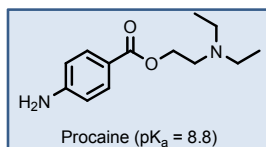


Lidocaine ( $pK_a = 7.8$ )

- Bio-isoteric analogue of isogramine (1946).
- Long-lasting local anesthetic properties compared to procaine (**Steric & electronic factors**).
- Nonirritating.
- Stable in aqueous solution.

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21



Procaine ( $pK_a = 8.8$ )

## Pharmaceutical Preparations

- Factors:
  - ✓ **Chemical stability (sterilization!!).**
  - ✓ **Aqueous solubility.**
- Dosage forms:
  - ✓ **Parenteral injections.**
  - ✓ **Topical applications.**

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22

## Toxicity & Side Effects

- Na and K channels in excitable membranes.
- Neuromuscular junctions, CNS, and CVS.
- Convulsions and CNS depression.
- PABA-induced allergic reactions.
- Depending on:
  - ✓ **Route and site of administration.**
  - ✓ **Lipid solubility.**
  - ✓ **Metabolic stability.**

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23

## Mechanism of Action of Local Anesthetics

- Act on membrane-bound sodium channels.
- Decrease excitability of nerve membranes.
- Block nerve conductance.
- Loss of sensation.

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24

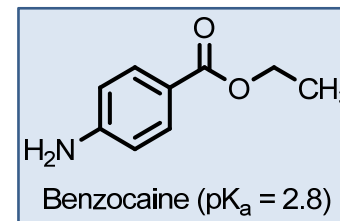
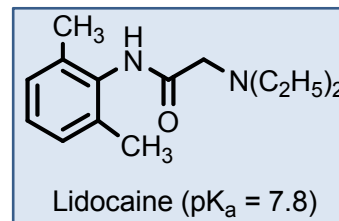
## pH Effect on the Local Anesthetic Activity

$$pH = pK_a - \log[BH^+] / [B]$$

- Tertiary amines ( $pK_a = 7.0$  to  $9.0$ ).
- Physiological  $pH = 7.4$ .
- Both  $[BH^+]$  and  $[B]$  are available for binding to the channel proteins.
- Which one is active????

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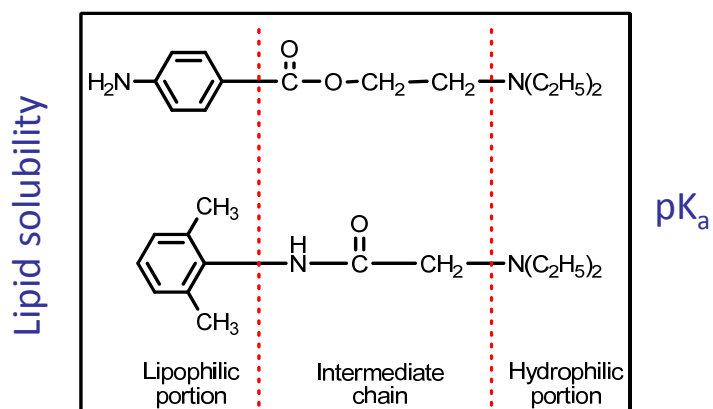


- Blocking actions of lidocaine:
  - ✓ 90% from  $[BH^+]$ .
  - ✓ 10% from  $[B]$ .
- Two binding sites:
  - ✓ Hydrophilic binding site.
  - ✓ Hydrophobic binding site (benzocaine).

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26

## Structure Activity Relationship (SAR)

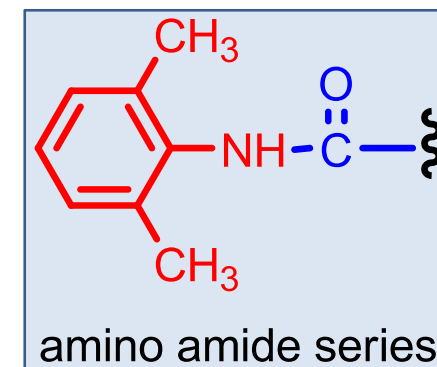
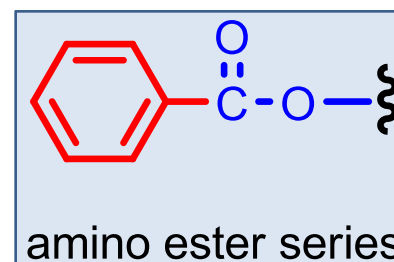


### Metabolic inactivation

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27

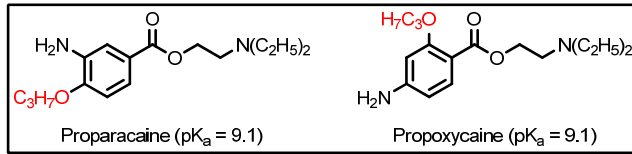
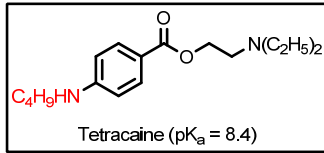
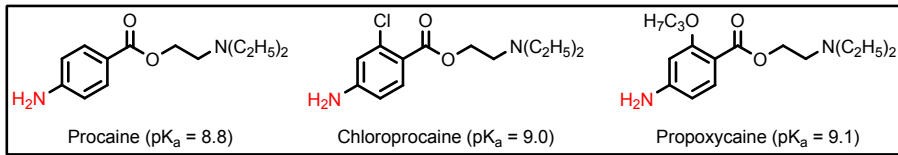
## Modification of the Lipophilic Portion



- Determines physical and chemical properties!

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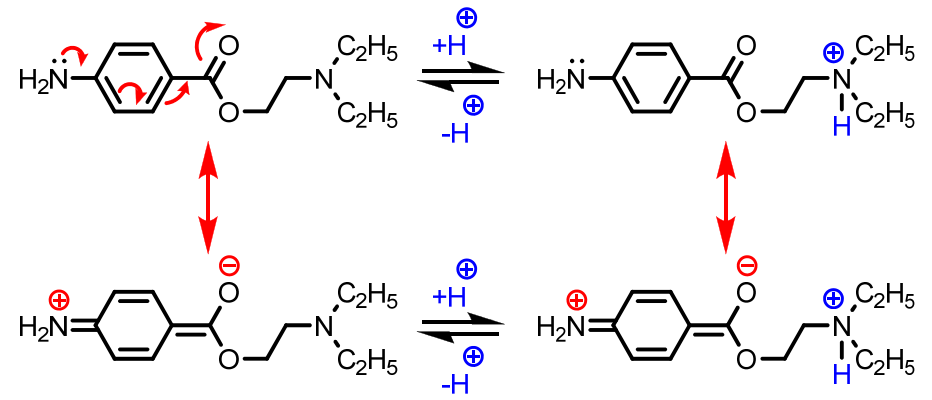
28



- Electron-donating substituent increases local anesthetic potency (**ortho & para**).

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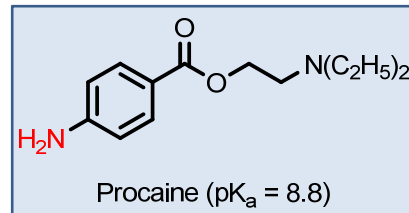
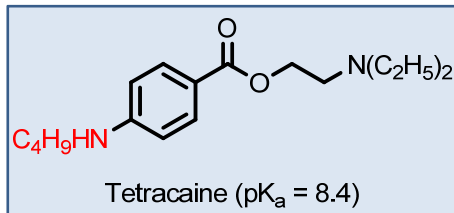
29



- Enhancement of zwitterion formation.
- Greater affinity for the receptor.
- Two binding patterns.

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30

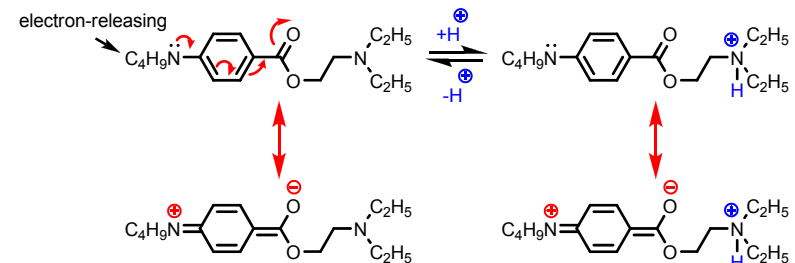
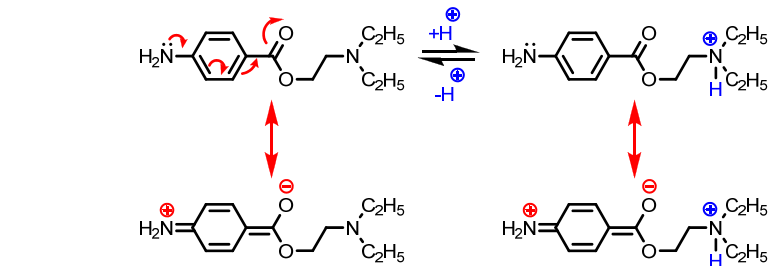


- Tetracaine is 50-fold more potent than procaine due to:

- ✓ Increasing lipid solubility.
- ✓ Electron-releasing property (zwitterion).

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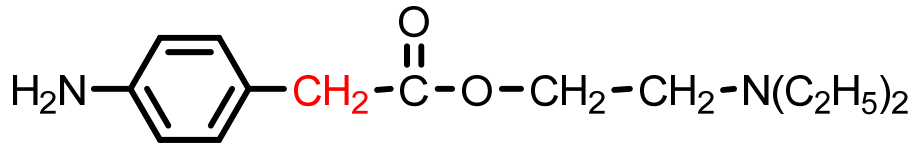
31



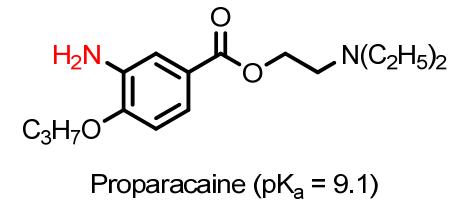
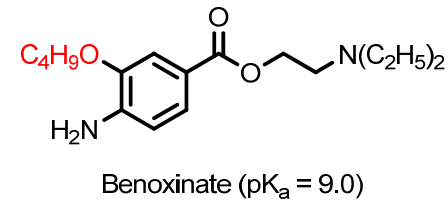
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32

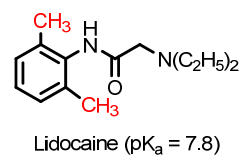
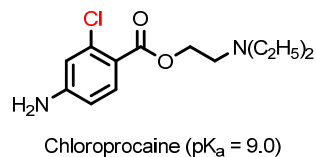
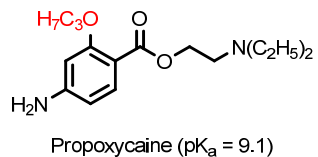




- Greatly reduced anesthetic potency.
- Prohibits the formation of the zwitterionic form.

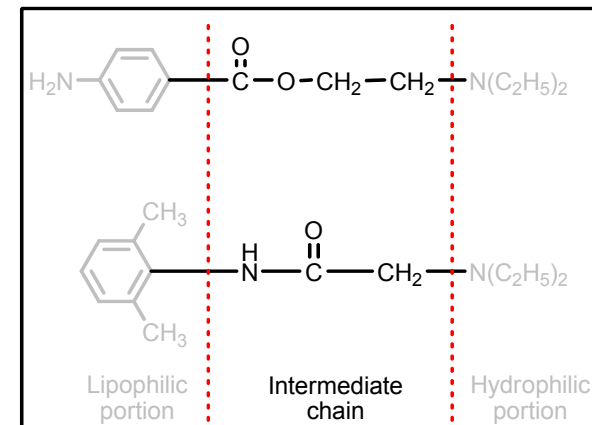


- Meta substituents only affect the lipophilicity.
- Zwitterionic form!!!???



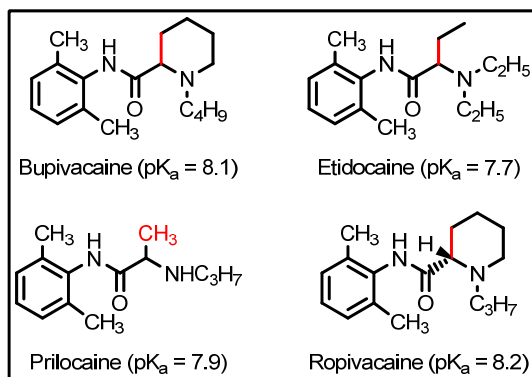
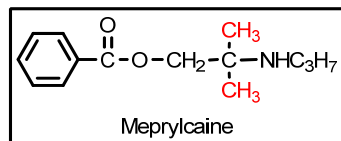
- Duration of action:
  - ✓ Long duration: propoxycaine & lidocaine.
  - ✓ Short duration: Chloroprocaine.
- Depending on ease of hydrolysis.

## Modification of the Intermediate Chain



- It influences the duration of action and relative toxicity.

## Modification of the Intermediate Chain

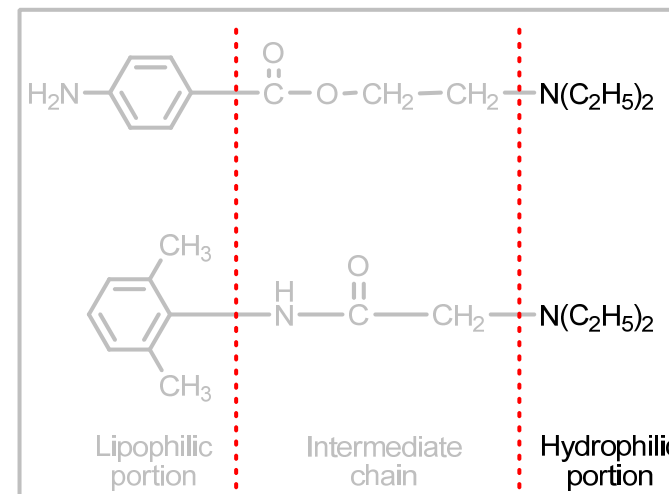


- Esterase- and amidase-catalyzed hydrolysis are hindered (long duration of action).

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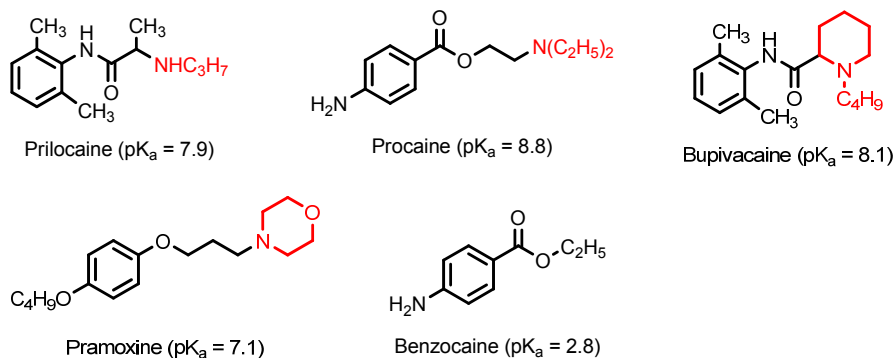
37

## Modification of the Hydrophilic Portion



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38

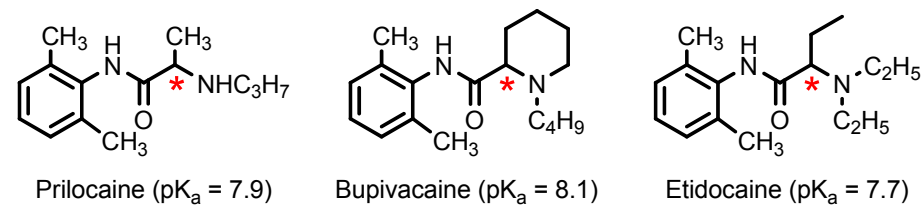


- Formation of water-soluble salt.
- Binding to the receptors (hydrophilic site).

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39

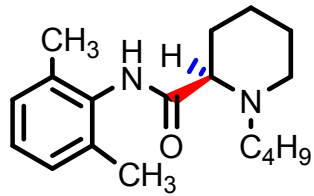
## Stereochemistry



- No stereochemical requirements for the local anesthetic activity (so far).
- Toxicity!

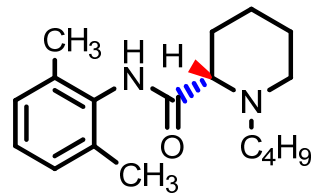
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40



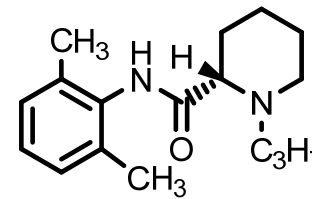
R-(+)-Bupivacaine ( $pK_a = 8.1$ )

- Cardiac toxicity.



Levobupivacaine ( $pK_a = 8.1$ )

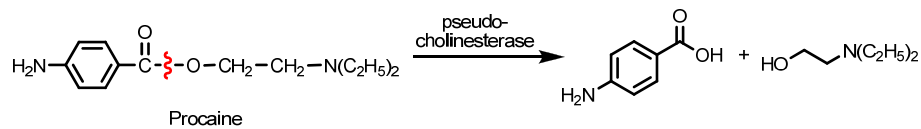
- No cardiac toxicity.
- Chiral switching!!!



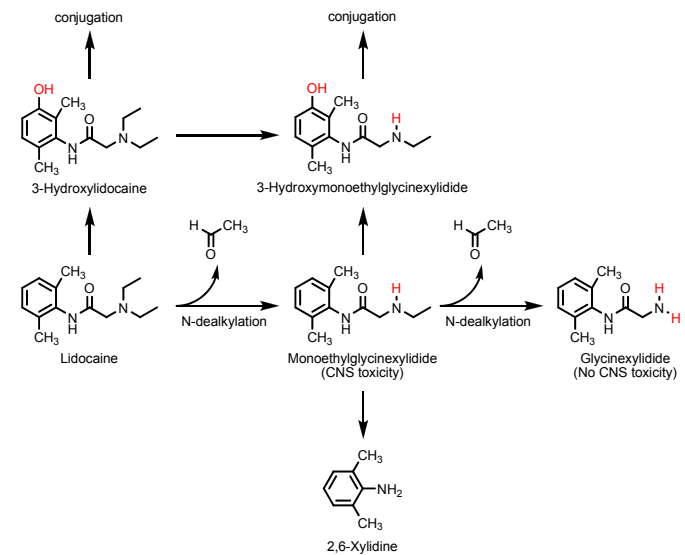
Ropivacaine ( $pK_a = 8.2$ )

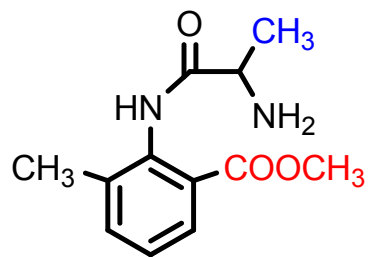
- Marketed as optically active local anesthetics.
- Lower cardiac toxicity.

## Metabolism of Local Anesthetics

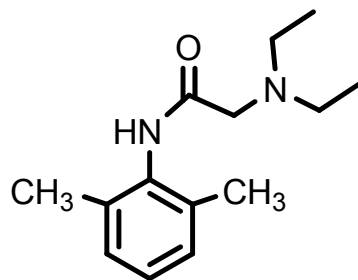


## Metabolism of Local Anesthetics





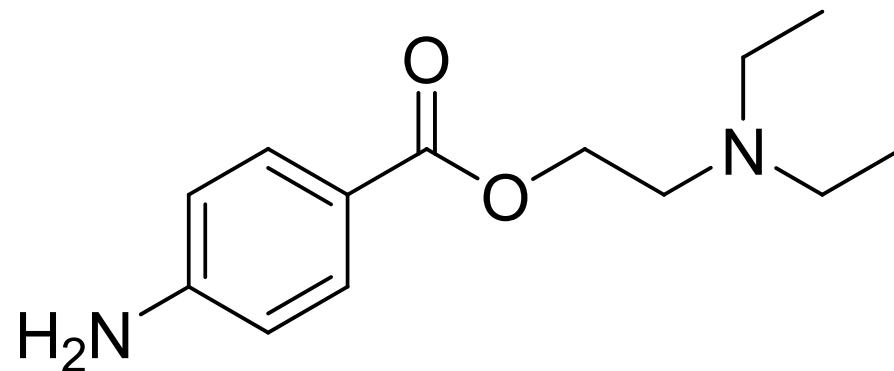
Tocainide



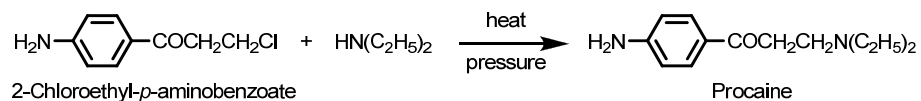
Lidocaine

- Good anesthetic activity.
- No CNS side effects.
- Clinically used as antiarrhythmic agent.

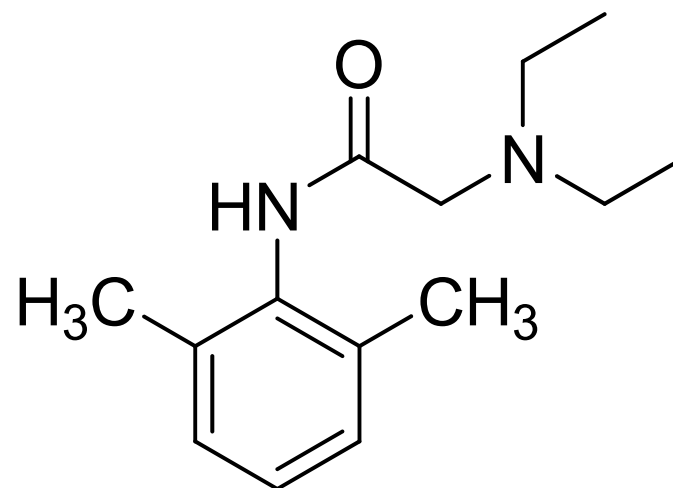
## Retrosynthesis of Procaine!



## Synthesis of Procaine



## Retrosynthesis of Lidocaine!



## Synthesis of Lidocaine

