Labs #7 and #8

Synthesis of Lidocaine

A crystalline solid usually administered as an aqueous solution of the hydrochloride salt as a local anesthetic.
Structure/Activity Relationships

![Chemical Structures]

**cocaine**
{natural product}

**lidocaine (xylocaine)**
{synthesized}

**generalized structure**

**structural components**
{aromatic, hydrocarbon, carbonyl, amine}
Two-step synthesis of lidocaine:

1. **Starting Material**: 2,6-dimethylaniline
   - Reaction with chloroacetyl chloride
   - Product: α-chloro-2,6-dimethylacetanilide

2. **Intermediate**: α-chloro-2,6-dimethylacetanilide
   - Reaction with diethylamine
   - Product: Lidocaine
Synthesis – Step #1

Step #1 - formation of a solid amide by NAS

- Formation of a solid amide by NAS
- Nucleophilic Acyl Subst.
- NaO₂CCH₃ stays in solution until sodium acetate has been added
- CH₃CO₂H + NaCl + solid amide ppt.

stays in solution until sodium acetate has been added
Chemistry of Carboxylic Acids & Derivatives

ArNH₂

NaNO₂

[ArN₂⁺]

R-X

CuCN

NaCN

RC≡N

H₂O

P₂O₅

{R' = H}

RCH₂NH₂

LiAlH₄

LiAlH₄

R'₂NH

R₂NH

SOCl₂

H₂O

LiAlH₄

LiAlH₄

RCH₂OH

NaBH₄

LiAlH₄

LiAlH₄

[O]

RCO₂Na

ArH

AlCl₃

R₂CuLi

LiAlH[OtBu]₃

PCC

NaBH₄
Organic Chemistry II - Lab

Labs #7 and #8

Synthesis of Lidocaine

Week #2
Two-step synthesis of lidocaine:

2,6-dimethylaniline \[ \xrightarrow{\text{ClCH_2COCl}} \] \[ \xrightarrow{\text{HN\textsubscript{Et}_2}} \] lidocaine

nucleophilic acyl substitution versus \( \text{S}_\text{N}2 \)
Reaction Scheme – Step #2

Step #2 - formation of lidocaine by an $S_{N2}$ reaction
Calculation of Et₂NH Required

Use **3 moles** diethylamine per 1 mole of α-chloro-2,6-dimethylacetanilide:

\[
\frac{\text{g "acetanilide"}}{197.66 \text{ g/mol "acetanilide"}} \times \frac{3 \text{ moles Et}_2\text{NH}}{1 \text{ mole "acetanilide"}} \times \frac{73.14 \text{ g/mol Et}_2\text{NH}}{0.71 \text{ g/mL Et}_2\text{NH}}
\]

- Volume of Et₂NH required should be **0.1-0.6 mL**.
Procedural Points

- Why is sodium acetate used in step #1?

- Why are anhydrous conditions needed in both steps? (What side-reactions occur with H₂O?)

- Why do we use a three-fold excess of diethylamine in step #2?

- Why do we use toluene as a solvent in step #2 and reflux for 45 minutes?

- What is the purpose of the acid extraction in step #2?
Isolation of Lidocaine Product

Acid extraction is used to remove lidocaine from the toluene solution:

- Lidocaine dissolved in toluene
  - HCl acid extraction
  - Lidocaine hydrochloride salt extracted into aqueous layer
  - KOH
  - Lidocaine (forms oily layer on top of aqueous base solution)
  - Cool
  - Crude lidocaine solid