A Semi-Synthetic Penicillin

2-phenoxyethanol \rightarrow Penicillium mold \rightarrow penicillin V
Gabriel Synthesis of a Primary Amine

RCH$_2$Br (alkyl halide) $\xrightarrow{\text{Gabriel synthesis}}$ RCH$_2$NH$_2$ (primary amine)

Phthalamide $\xrightarrow{\text{H}_2\text{O}^-}$ an N-substituted imide $\xrightarrow{\text{R-Br, } S_N^2}$ phthalic acid + primary alkyl ammonium ion

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A Nitrile

acetonitrile
# Nomenclature of Nitriles

<table>
<thead>
<tr>
<th>Systematic Name</th>
<th>Common Name</th>
<th>Structural Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>ethanenitrile</td>
<td>acetonitrile, methyl cyanide</td>
<td>CH$_3$C≡N</td>
</tr>
<tr>
<td>benzenenitrile</td>
<td>benzonitrile, phenyl cyanide</td>
<td>C$_6$H$_5$C≡N</td>
</tr>
<tr>
<td>5-methylhexanenitrile</td>
<td>δ-methylcapronitrile, isohexyl cyanide</td>
<td>CH$_3$CHCH$_2$CH$_2$CH$_2$C≡N</td>
</tr>
<tr>
<td>propenenitrile</td>
<td>acrylonitrile</td>
<td>CH$_2$═CHC≡N</td>
</tr>
</tbody>
</table>

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Acid-Catalyzed Hydrolysis of a Nitrile

\[
\text{RC≡N} \xrightarrow{\text{HCl, H}_2\text{O}} \xrightarrow{\Delta} \text{RCOOH}
\]
The Mechanism

R-C≡N$^-$ $\xrightarrow{H-B^+}$ R-C≡NH$^+$ + H$_2$O$^-$ $\xrightarrow{\text{several steps}}$ R-C-OH$^+$ (a carboxylic acid)

Oxygen loses a proton

Nitrogen gains a proton

Resonance contributors for a protonated amide
Synthesis of a Carboxylic Acid

\[
\text{CH}_3\text{CH}_2\text{Br} \xrightarrow{\text{DMF}} \text{CH}_3\text{CH}_2\text{C}≡\text{N} \xrightarrow{\text{HCl, H}_2\text{O}} \text{CH}_3\text{CH}_2\text{COOH}
\]
Synthesis of a Primary Amine

\[ \text{RC≡N} \xrightarrow{\text{H}_2, \text{Raney nickel}} \text{RCH}_2\text{NH}_2 \]
An Acid Anhydride
An Acid Anhydride is Formed When Water is Lost from Two Molecules of a Carboxylic Acid.
Nomenclature of Acid Anhydrides

- **Systematic name:** ethanoic anhydride
- **Common name:** acetic anhydride
- **Ethanoic methanoic anhydride**
  - Form: a symmetrical anhydride
  - Form: a mixed anhydride
Acid Anhydrides are Less Reactive Than Acyl Chlorides but More Reactive Than Esters
Reactions of Acid Anhydrides

\[
\text{RCO}_2\text{OCR} + \text{CH}_3\text{CH}_2\text{OH} \rightarrow \text{RCO}_2\text{OCH}_2\text{CH}_3 + \text{RCO}_2\text{OH}
\]

\[
\text{RCO}_2\text{OCR} + \text{H}_2\text{O} \rightarrow 2\text{RCO}_2\text{OH}
\]

\[
\text{RCO}_2\text{OCR} + 2\text{CH}_3\text{NH}_2 \rightarrow \text{RCO}_2\text{NHCH}_3 + \text{RCO}_2\text{O}^- \text{H}_3\text{NCH}_3^+
\]
The Mechanism
Analgesics

- **Morphine**
- **Codeine**
- **Heroin**
# Dicarboxylic Acids

<table>
<thead>
<tr>
<th>Dicarboxylic acid</th>
<th>Common name</th>
<th>$pK_{a1}$</th>
<th>$pK_{a2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Oxalic acid" /></td>
<td>Oxalic acid</td>
<td>1.27</td>
<td>4.27</td>
</tr>
<tr>
<td><img src="image" alt="Malonic acid" /></td>
<td>Malonic acid</td>
<td>2.86</td>
<td>5.70</td>
</tr>
<tr>
<td><img src="image" alt="Succinic acid" /></td>
<td>Succinic acid</td>
<td>4.21</td>
<td>5.64</td>
</tr>
<tr>
<td><img src="image" alt="Glutaric acid" /></td>
<td>Glutaric acid</td>
<td>4.34</td>
<td>5.27</td>
</tr>
<tr>
<td><img src="image" alt="Adipic acid" /></td>
<td>Adipic acid</td>
<td>4.41</td>
<td>5.28</td>
</tr>
<tr>
<td><img src="image" alt="Phthalic acid" /></td>
<td>Phthalic acid</td>
<td>2.95</td>
<td>5.41</td>
</tr>
</tbody>
</table>

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The Two $pK_a$ Values of Dicarboxylic are Different

Why?
The neighboring COOH group withdraws electrons and lowers the first $pK_a$. Electrostatic interaction between like charges raises the second $pK_a$. 
Dicarboxylic Acids Lose Water When Heated if They Can Form a Five- or Six-Membered Ring

\[
\text{glutaric acid} \xleftrightarrow{\Delta} \text{glutaric anhydride}
\]

\[
\text{phthalic acid} \xleftrightarrow{\Delta} \text{phthalic anhydride} + \text{H}_2\text{O}
\]
Acetic Anhydride (or Acetyl Chloride)
Catalyzed Anhydride Formation

\[
\text{succinic acid} + \text{acetic anhydride} \xrightarrow{\Delta} \text{succinic anhydride} + 2 \text{acetate}
\]
Many Synthetic Polymers Contain Amide and Ester Linkages

- **Dacron**:
  \[
  \text{OCH}_2\text{CH}_2\text{O} \quad \text{C} \quad \text{C} \quad \text{CH}_2\text{CH}_2\text{O}
  \]

- **nylon 6**: (amidic polymer with repeating amide groups)

- **Kevlar**: Polymeric aromatic amide of 4,4'-diaminodiphenyl methane and terephthalic acid

- **Lexan**: Polycarbonate polymer with repeating carbonate (COO) groups
Activating Carboxylic Acids by Converting Them to Acyl Chlorides

\[
\begin{align*}
\text{RCOO}^- + \text{SOCl}_2 & \xrightarrow{\Delta} \text{RCOCl} + \text{SO}_2 + \text{Cl}^- \\
\text{RCOO}^- + \text{PCl}_3 & \xrightarrow{\Delta} \text{RCOCl} + \text{OPCl}_2
\end{align*}
\]
These Reagents Give the Carboxylic Acid a Better Leaving group Than Chloride Ion

\[
\begin{align*}
\text{R-C-Cl} & \quad \text{PCl}_2 \\
\text{R-C-O-Cl} & \quad \text{good leaving groups}
\end{align*}
\]

\[
\begin{align*}
\text{R-C-Cl} & \quad \text{SO}_2 + \text{Cl}^- \\
a \text{better leaving group than a chloride ion}
\end{align*}
\]
Starting with an Acyl Chloride a Wide Variety of Carboxylic Acid Derivatives Can Be Synthesized

\[
\begin{align*}
\text{RCOCl} + \text{RO}^- & \rightarrow \text{RCOOR} + \text{Cl}^- \\
\text{RCOCl} + \text{ROH} & \rightarrow \text{RCOOR} + \text{HCl} \\
\text{RCOCl} + 2\text{RNH}_2 & \rightarrow \text{RCO}\text{NHR} + \text{R}_2\text{NH}\text{Cl}^- \\
\end{align*}
\]
Activating Carboxylic Acids by Converting Them to Acid Anhydrides

$$2 \text{RC(OH)} \overset{P_2O_5}{\longrightarrow} \text{RC(OCR)} + H_2O$$
Heating Phosphoric Acid Forms Pyrophosphoric Acid and Triphosphoric Acid

\[ \text{phosphoric acid} \xrightarrow{\Delta} \text{pyrophosphoric acid} + \text{triposphoric acid} + 3\text{H}_2\text{O} \]
ATP
Mixed Anhydrides of a Carboxylic Acid and a Phosphoric Acid

an acyl phosphate
mixed anhydrides
an acyl adenylate
Forming an Acyl Phosphate

\[
\text{\textit{\gamma}-phosphorus} \quad \text{a phosphoanhydride bond}
\]

\[
\text{adenosine triphosphate (ATP)} \quad \text{enzyme} \quad \text{an acyl phosphate} \quad \text{adenosine diphosphate (ADP)}
\]
Forming an Acyl Adenylate

adenosine triphosphate (ATP) + enzyme → an acyl adenylate + pyrophosphate
The Negative Charges on ATP are Neutralized at the Active Site of an Enzyme
A Thioester is More Susceptible to Nucleophilic Addition Than an Oxygen Ester

\[
\begin{align*}
\text{a thioester} & \quad \text{CH}_3\text{CH}_2\text{SH} \quad pK_a = 10.5 \\
\text{an oxygen ester} & \quad \text{CH}_3\text{CH}_2\text{OH} \quad pK_a = 15.9
\end{align*}
\]
Coenzyme A is the thiol used in cells.
A Carboxylate Ion is First Converted to an Acyl Adenylate and Then to a Thioester

\[
\begin{align*}
\text{CH}_3\text{C}^- & + \text{ATP} \xrightarrow{\text{enzyme}} \text{CH}_3\text{C}^\text{Ad}^- + \text{pyrophosphate} \\
\text{CH}_3\text{C}^\text{Ad}^- & + \text{CoASH} \rightarrow \text{CH}_3\text{C}^\text{SCoA}^- + \text{AMP}
\end{align*}
\]
Using Acetyl-CoA to Form Acetylcholine

\[
\text{acetyl-CoA} + \text{choline} \xrightarrow{\text{enzyme}} \text{acetylcholine} + \text{CoASH}
\]