Synthesis of a local anesthetic
Benzocaine

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Figure 1: Benzocaine

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1 Synthesis of Benzocaine

1.1 Method [4]

I synthesized a local anesthetic called Benzocaine (Fig. 1 on page i).

Benzocaine was prepared in this experiment by the direct esterification of p-Aminobenzoic acid with absolute ethanol.

See the following chart (Fig. 2) for the reaction.

![Figure 2: Reaction](image)

<table>
<thead>
<tr>
<th>Number</th>
<th>Compound</th>
<th>Molar mass [g mol⁻¹]</th>
<th>Density [g cm⁻³]</th>
<th>Refraction index [n²₀]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-Aminobenzoic acid</td>
<td>137</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Ethanol</td>
<td>46</td>
<td>0.791</td>
<td>1.362</td>
</tr>
<tr>
<td>3</td>
<td>Sulfuric acid</td>
<td>98</td>
<td>1.83</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Sodium Carbonate</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Benzocaine</td>
<td>165</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Physical Data

1.1.1 Mechanism [10], [7], [9]

Like the direct esterification reaction to produce artificial flavors, this reaction gives a lower yield of Benzocaine due to chemical equilibrium. But by Le Chatelier’s principle, the equilibrium of the reaction is shifted to yield additional product. Due to this principle the balance is on the side of the lower force, and consequently on the water side. This is why the water has to be removed by toluene in an azotropes distillation.

The accepted mechanism (Fig. 3 on page 2) of the reaction follows and involves (1) the protonation of the carboxylic acid by the acid catalyst to give
the resonance-stabilized intermediate I, followed by (2) the nucleophilic attack of the alcohol. The subsequent transfer of the proton (3), loss of water (4), and loss of proton (5) then give the final observed products. The reverse reaction to yield the carboxylic acid and alcohol follows the same steps in the opposite order.

\[ \begin{align*}
\text{H}_2\text{N} & \text{C} \text{H} \text{H} \text{C} \text{H} \text{N} \text{H} \text{C} \text{H} \text{C} \text{H} \text{C} \text{H} \text{C} \text{H} \text{C} & \text{O} \\
\text{O} & \text{H} & \text{O} & \text{C} \text{H} \text{C} \text{H} \text{C} & \text{H} & \text{C} \text{H} \\
\text{H}_2\text{N} & \text{C} \text{H} \text{H} \text{C} \text{H} \text{C} \text{H} \text{C} \text{H} \text{C} \text{H} \text{C} & \text{O} & \text{H} & \text{O} & \text{C} \text{H} \text{C} \text{H} \text{C} & \text{H} & \text{C} \text{H} \\
\end{align*} \]

Figure 3: Mechanism

The reaction workup involves first making the reaction mixture alkaline with sodium carbonate solution. With this step, all the following reactions occur. (Fig. 4 on page 3 and Fig. 5 on page 4)

Because the amount of sodium carbonate solution added is not very large, roughly an equal volume of water and ethanol results. Under these conditions, much of the nonionic benzocaine formed in the experiment should remain dissolved, and some ionic sodium bisulfate and unreacted sodium \( p \)-aminobenzoate may precipitate. Extraction of the mixture with ether permits the separation of the benzocaine from the ionic compounds. Then after the ether–ethanol layer is dried and evaporated, crystallization of the resulting oil from an ethanol–water solution further purifies the benzocaine.

Benzocaine is unlike the other local anesthetics in not having a secondary or tertiary amino group separated from the aromatic portion of the molecule. It also does not suffuse well into tissue, this making it unsuitable for injection but useful as a skin preparation. Its low water solubility and consequent slow absorption from the area of application are beneficial in producing a lower level of toxicity and a longer period of anesthetic protection.

1.2 Experimental part

In table 2 all used compounds are listed.

2.7 grams (0.020 mole) of \( p \)-aminobenzoic acid were placed in a 100 ml round-bottom flask. 25 ml (0.60 mole) of pure, absolute ethanol, were added with

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2See [1] for further information, please.
1 SYNTHESIS OF BENZOCAINE

\[ \text{H}_2\text{SO}_4 + \text{Na}_2\text{CO}_3 \rightarrow \text{Na}_2\text{SO}_4 + \text{H}_2\text{O} + \text{CO}_2 \]

Unreacted starting material

\[ \text{H}_2\text{N} \quad \text{C} \quad \text{O} \quad + \text{3 Na}_2\text{CO}_3 \quad \rightarrow \quad \text{H}_2\text{N} \quad \text{C} \quad \text{O} \quad + \text{2 Na}_2\text{SO}_4 \quad + \text{3 H}_2\text{O} \quad + \text{3 CO}_2 \]

Sodium p-aminobenzoate

Figure 4: Mechanism

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mass [g] or Volume [ml]</th>
<th>Moles [mole]</th>
<th>Origin</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Aminobenzoic acid</td>
<td>2.7 g</td>
<td>0.020</td>
<td>Fluka</td>
<td>purum</td>
</tr>
<tr>
<td>Ethanol</td>
<td>35 ml</td>
<td>0.6</td>
<td>Fluka</td>
<td>purum</td>
</tr>
<tr>
<td>Sulfuric acid</td>
<td>2.5 ml</td>
<td>0.045</td>
<td>Fluka</td>
<td>purum</td>
</tr>
<tr>
<td>Sodium Carbonate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Used compounds

gently stirring to help dissolve most of the solid. The mixture was cooled in an ice bath and 2.5 ml (0.045 mole) of concentrated sulfuric acid were slowly added. A large amount of precipitate formed, but slowly dissolved when the mixture was refluxed. A reflux condenser was attached and the mixture was heated under reflux for 2 hours. During this time, the mixture was swirled approximately every 5 to 10 minutes until the solid dissolves.

The contents of the flask were poured into a 250 ml beaker, cooled to room temperature, and a 20% sodium carbonate solution was slowly added in small portions with stirring. After each addition, an extensive evolution of gas occurred until the acid was nearly neutralized. When additional sodium carbonate solution produced no more gas, the pH of the solution was checked with pH paper and indicated to be neutral.

The ethanol–water mixture was carefully decanted from its precipitate present into a separatory funnel. 25 ml of anhydrous ethyl ether were added to any precipitate in the beaker and the solution was stirred. Then this ether was de-
Figure 5: Mechanism

canted from any remaining precipitate into the separatory funnel. This ensured that no benzocaine was lost from the water having been added.

The ether, water, and ethanol mixture was shaken in the separatory funnel, and the lower aqueous layer was drawn off into an Erlenmeyer flask and the aqueous layer was poured back into the separatory funnel. The aqueous layer was extracted with another 25 ml of ether and both ether layers were combined.

The ether–ethanol solution was dried with anhydrous magnesium sulfate, then the drying agent was removed by gravity filtration. The ether and ethanol were evaporated in the hoof, using the rotavap. Hot 95% ethanol was slowly added and the mixture was heated until the oil dissolved. Then hot water was slowly added to the alcohol solution until extensive cloudiness or the oil appears.

The mixture was cooled in an ice bath with swirling. During the cooling, any oil initially present solidified. The crystals of purified benzocaine were collected by suction filtration.

The results are given in table 3. Important physical data points are given in table 4.
1 SYNTHESIS OF BENZOCAINE

Final weight 2.1 g
Mole 0.013 mole
Yield 65 %

Table 3: Results

1.2.1 Yield

1.3 Physical data

Melting point 89-92 °C
Density \( \frac{\text{g}}{\text{cm}^3} \)

Table 4: Physical data [6]

1.4 Results

1.4.1 IR Spectra

The infrared spectra was obtained in a KBr pellet, with 50mg of product (5%) on 0.95g of KBr. (See the added graphics showing the original KBr and a reference.

1.4.1.1 Results The infrared spectra shows specific peaks (table 5) being characteristic for my substance. Peaks being very important are marked with a ∗.

<table>
<thead>
<tr>
<th>Peak [( \frac{\text{cm}}{\text{cm}^2} )]</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>850</td>
<td>= C – H ( \delta )</td>
</tr>
<tr>
<td>1’170</td>
<td>C – O st.</td>
</tr>
<tr>
<td>1’300</td>
<td>C – N st.</td>
</tr>
<tr>
<td>∗ 1’660</td>
<td>Ar – C = C st.</td>
</tr>
<tr>
<td>1’700</td>
<td>N – H ( \delta )</td>
</tr>
<tr>
<td>∗ 2’400</td>
<td>O – H st.</td>
</tr>
<tr>
<td>2’950</td>
<td>C – H st.</td>
</tr>
<tr>
<td>3’250</td>
<td>N – H st.</td>
</tr>
<tr>
<td>∗ 3’450</td>
<td>O – H st.</td>
</tr>
</tbody>
</table>

Table 5: IR results [8]


1.5 Discussion

No problems occurred during the process.
1.6 Toxicology


<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>S</th>
<th>Poisonous category</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Aminobenzoic acid</td>
<td>22</td>
<td>24/25</td>
<td>CH4</td>
</tr>
<tr>
<td>Ethanol</td>
<td>11</td>
<td>7-16</td>
<td>CH3</td>
</tr>
<tr>
<td>Sulfuric acid</td>
<td>35</td>
<td>26-30-45</td>
<td>CH2</td>
</tr>
<tr>
<td>Sodium Carbonate</td>
<td>36</td>
<td>22-26</td>
<td>CH5</td>
</tr>
<tr>
<td>Benzocaine</td>
<td>43</td>
<td>24/25-37</td>
<td>CH4</td>
</tr>
</tbody>
</table>

Table 6: Toxicology [3]

<table>
<thead>
<tr>
<th>Type</th>
<th>Number</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>11</td>
<td>Highly flammable</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>Harmful if swallowed</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>Causes severe burns</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>Irritating to eyes</td>
</tr>
<tr>
<td></td>
<td>43</td>
<td>May cause sensitization by skin contact</td>
</tr>
<tr>
<td>S</td>
<td>7</td>
<td>Keep container tightly closed</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>Keep away from sources of ignition – No smoking</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>Do not breathe dust</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>Avoid contact with skin</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>Avoid contact with eyes</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>In case of contact with eyes, rinse immediately with plenty of water and seek medical advice</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>Never add water to this product</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>Wear suitable gloves</td>
</tr>
</tbody>
</table>

Table 7: R– and S–phrases

Concentrated sulfuric acid is extremely hazardous and corrosive. Handle it with care.

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Swiss profile:
1. cancerogen, mutagen, teratogen
2. very intense poison
3. intense poison
4. no harmless product
5. harmless product
References


Figure 6: Original IR spectra of Benzocaine
Figure 7: Reference IR spectra of Benzocaine