The Synthesis of the Anticonvulsant Dilantin

Adapted by R. Minard and J. Klopp and W. Gerhardt from an Exp't used at Lycoming College

Introduction:

In 1838, the German chemist, Justus Liebig reported the discovery of dilantin(1). It was not uncovered, however, until 100 years later that dilantin is an anticonvulsant. This property is currently exploited in the treatment of epilepsy.

Dilantin can be formed in a two step synthesis. First, benzoin (1) is oxidized to benzil (2) via Cu$^{2+}$ catalysis.

\[
\begin{align*}
\text{benzoin 1} & \xrightarrow{\text{copper acetate}} \text{benzil 2} \\
+ 2\text{NH}_4\text{NO}_3 + 3\text{CH}_3\text{COOH} & \xrightarrow{\text{Cu(OCOCH}_3\text{)}_2} + 2\text{NO} + 4\text{H}_2\text{O} + 2\text{NH}_4\text{OCOCH}_3
\end{align*}
\]

The second step is a base induced rearrangement of benzil (2) to benzilic acid followed by condensation with urea (3) and then protonation by acidification to yield dilantin. This is the reaction that will be carried out here.

\[
\begin{align*}
\text{benzil 2} + \text{H}_2\text{NCONH}_2 & \xrightarrow{\text{1. NaOH}} \text{Dilantin 4} + 2\text{H}_2\text{O} \quad \text{2. HCl}
\end{align*}
\]

Caution:

HCl is a corrosive acid while NaOH is a corrosive base. Flush spills with a lot of water. Handle with care and wash hands afterwards.

Synthesis of Dilantin:

Place 2 g of benzil, 30 mL of 95% ethanol, 6 mL of a 30% (w/v) aqueous NaOH solution (prepared by mixing 1.8 g of NaOH pellets with 6 mL water), and 1 g of urea into a 100-mL round bottom flask along with a 1” stir bar. Attach a condenser and clamp the flask in heating mantle (no sand!) over a stir plate. Heat the reaction at a gentle reflux with stirring for 1.5 hours.

Isolation and Purification of Dilantin:

Remove the heat and let the reaction mixture cool until it feels still quite warm to the touch. *Note*– allowing the flask to cool too much will cause the crystals to form while still in the flask. Add 40 mL of water and remove any insoluble particles by vacuum filtration using a Buchner funnel and 125-mL filter flask. Transfer the filtrate to a 250 mL beaker and add 6M HCl dropwise until crystals cease forming and the solution tests acidic. Collect the product by vacuum filtration and wash it with small portions of water. Recrystallize the product from the minimum amount of 95% ethanol. After the crystals have dried, determine their weight and % yield, obtain a melting point and 1H and 13C NMR, IR spectra and GC-MS.

Cleaning Up:

Aqueous solutions and ethanol can be flushed down the drain with water. The organic solvents should be placed into the non-halogenated waste container.

Analysis:

Take a melting point and acquire all spectra data of the product, Dilantin.

Final Report:

Attached all spectra, with structures and interpretation on them. Write the equation for the reaction that occurs during the acidification of the basic reaction solution to precipitate Dilantin. Include these items in the Discussion section of the final report.