Dilantin—an Antiepileptic Drug by a Biomimetic Synthesis

48.1 Introduction

This chapter describes the synthesis of the antiepilepsy drug dilantin. First, however, a few words about the causes of epilepsy and its control.

In the body a signal from a sensory organ is transmitted along a nerve fiber until it reaches the end of the cell, called the synapse. At the synapse the arriving electrical signal induces the release of a chemical neurotransmitter that diffuses across the synaptic gulf, a short distance of about 100 Å that separates the end of one nerve cell and the beginning of another, where it triggers electrical signal in the next nerve fiber. Thus, nerve transmission is a combination of chemical and electrical signals.

In the brain many simultaneous signals are involved and the signal flow is controlled, in part, by the plasma level of gamma aminobutyric acid (GABA). The GABA level, to offer a simplistic analogy, is like the gain control on a public address system in an auditorium. If the GABA level is high, the gain of the nervous system is low; low GABA levels produce high gains and increased sensitivity to small signals. In the public address system, if the gain is too high, even the smallest output feeds back to the input microphone and the system breaks into uncontrolled squeals. In animals the equivalent to the squeal is a random, uncontrolled firing of neurons that induce violent spastic movements. This apparently is what happens in at least some forms of epileptic seizures and is associated with lower than normal levels of GABA in the brain. One might hope to control the seizures by administering GABA, but this fails because GABA does not pass the blood–brain barrier. Instead, one can take advantage
of the fact that much of the natural GABA is adsorbed on cell walls; if it is displaced by some agent, the level of GABA in the plasma can rise to an adequate control level.

In 1938 a compound that controls epileptic convulsions in this fashion was discovered. This material, now called dilantin, proved particularly valuable because in ordinary doses it is not a sedative and does not impair consciousness, unlike phenobarbital that had been used earlier.

You will be preparing dilantin by the three-step synthesis shown next. As it happens, each of these steps contains some particularly pretty chemistry that will be described separately in the next few sections.

\[
2 \text{C}_6\text{H}_5\text{C} = \text{H} \xrightarrow{\text{NaCN}} \text{C}_6\text{H}_5\text{C} = \text{C} \xrightarrow{} \text{C}_6\text{H}_5\text{C} = \text{C} \text{C}_6\text{H}_5
\]

Benzaldehyde

\[
\text{C}_6\text{H}_5\text{C} = \text{C} \xrightarrow{\text{NH}_2\text{C} = \text{NH}_2} \text{C}_6\text{H}_5\text{C} = \text{C} \text{C}_6\text{H}_5
\]

Benzil

\[
\text{C}_6\text{H}_5\text{C} = \text{C} \xrightarrow{\text{NaCN}} \text{C}_6\text{H}_5\text{C} = \text{C} \text{C}_6\text{H}_5
\]

Dilantin

48.2 The Benzoin Condensation

Two molecules of an aromatic aldehyde, when heated with a catalytic amount of sodium or potassium cyanide in aqueous ethanol, react to form a new carbon–carbon bond between the carbonyl carbons. The product is an \(\alpha\)-hydroxy ketone (a class of compounds with the generic name benzoin).

\[
2 \text{C}_6\text{H}_5\text{C} = \text{H} \xrightarrow{\text{NaCN}} \text{C}_6\text{H}_5\text{C} = \text{C} \xrightarrow{} \text{C}_6\text{H}_5
\]

Benzoin

This remarkably facile condensation was discovered accidentally by Wohler and Liebig in 1832 when they attempted to extract the cyanohydrin of benzaldehyde with base to remove acid impurities.
The mechanism for cyanide-catalyzed benzoin formation involves a rather long sequence of steps. It starts with reversible addition of cyanide ion to the carbonyl group of one benzaldehyde to form the anion of the cyanohydrin (step 1), which in aqueous ethanol rapidly equilibrates with the neutral cyanohydrin (step 2). The acidity of the C—H bond adjacent to the cyano group is enhanced by resonance stabilization of the anion, and under the basic conditions of the reaction (NaCN is basic) the isomeric carbanion is formed (step 3). This adds to a second molecule of benzaldehyde (step 4); proton interchange and loss of cyanide ion (steps 5 and 6) lead to benzoin. The rate determining step appears to be step 4.
There are two requirements for an effective catalyst of the benzoin condensation. First, the catalyst must give significant amounts of carbonyl adduct (steps 1 and 2), but not form such a strong bond that the catalyst is not easily lost in the last step. Second, the catalyst must stabilize the anion sufficiently to allow the C—H bond to be broken readily, but not so much that the anion becomes unreactive. For more than a 100 years, the only species that had been found that satisfied these requirements was the cyanide ion. However, in 1958 Breslow discovered that the conjugate base of a thiazolium salt also was an effective catalyst; it added reversibly to aldehydes and stabilized the α-anion by resonance.
What gave Breslow’s study broader significance was his recognition that thiamine (vitamin B₁) contains a thiazole unit and that a number of important biochemical reactions requiring it as a coenzyme could be understood as analogs of the benzoin condensation.

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{P} \quad \text{O} \quad \text{P} \quad \text{O} \\
\text{O} & \quad \text{CH}_2\text{CH}_2 \\
\text{O} & \quad \text{S} \quad \text{H} \\
\text{CH}_3 & \quad \text{N} \quad \text{H} \\
\text{CH}_2 & \quad \text{N} \quad \text{H}_2 \\
\text{CH}_3 & \quad \text{N} \\
\end{align*}
\]

Thiamine pyrophosphate (Cocarboxylase)

The preparation of benzoin using thiamine hydrochloride as the catalyst is described next. The conversion of benzoin to benzil and the use of these compounds as intermediates for synthesis are discussed later.

**Benzoin.** In a 50-mL Erlenmeyer flask prepare a solution of 1.04 g (0.003 mole) of thiamine hydrochloride in 3 mL of water. When all of the thiamine hydrochloride was dissolved, add 8 mL of 95% ethanol, 3 mL of 10% sodium hydroxide (0.006 mole), and 3 mL (3.2 g, 0.03 mole) of benzaldehyde, with thorough mixing between each addition. Stopper the flask and allow it to stand at room temperature at least overnight (longer periods do no harm).

At the end of the reaction period, the benzoin should have separated as fine crystals. Cool the flask in an ice-water bath to complete the crystallization, collect the product on a Hirsch funnel, and wash the crystals thoroughly with two 7-mL portions of cold 50% ethanol and several portions of water. Press the crystals as dry as possible and spread them on a fresh filter paper to dry in the air. The yield is 1.8–2.2 g (dry weight).

The product may be used without careful drying or recrystallization, for the preparation of derivatives or for conversion to benzil or benzilic acid. Benzoin may be purified, with a loss of 10–15%, by recrystallization from methanol (12 mL/g of benzoin) or from ethanol (8 mL/g). Determine the infrared spectrum of the purified product and demonstrate its purity by TLC.

### 48.3 Oxidation of Benzoin to Benzil

Benzoin can be oxidized to the diketone benzil in a number of ways, of which the most interesting is by a “coupled oxidation” using Cu^{+2} as the catalytic transfer oxidant. In a coupled oxidation the overall oxidation proceeds in two
distinct stages. In the present procedure, cupric acetate is used in catalytic amount (less than 1% of the stoichiometric requirement) and is continuously reoxidized from the reduced (cuprous) state by ammonium nitrate, which is present in excess. The latter is reduced to ammonium nitrite, which decomposes in the reaction mixture into nitrogen and water. It is convenient to represent this two-stage oxidation in the manner used by biochemists, who commonly deal with multiple coupled reactions.

\[
\begin{align*}
\text{NH}_4^+ \text{NO}_3^- & \quad \xrightarrow{\text{Cu}^{2+}} \quad \text{C}_6\text{H}_5\text{C} = \text{C} = \text{C}_6\text{H}_5 \\
\text{NH}_4^+ \text{NO}_2^- & \quad \xrightarrow{\text{Cu}^{+}} \quad \text{C}_6\text{H}_5\text{C} = \text{C} = \text{C}_6\text{H}_5
\end{align*}
\]

\[\text{N}_2 + 2 \text{H}_2\text{O}\]

Cupric salts are mild oxidizing agents that do not attack the diketone product. In the absence of Cu\(^{+2}\), ammonium nitrate will not oxidize benzoin (or benzil) at a significant rate. The reaction is general for \(\alpha\)-hydroxyketones (acylloins) and is the basis for the Fehling’s test for reducing sugars (Chapter 53).

**Oxidation of Benzoin by Cupric Salts.** In a 25-mL round-bottomed flask place 1.75 g (0.008 mole) of unrecrystallized benzoin, 5 mL of glacial acetic acid, 0.8 g (0.01 mole) of pulverized ammonium nitrate, and 1 mL of a 2% solution of cupric acetate.\(^1\) Add one or two boiling chips, attach a reflux condenser equipped with a gas trap (see Figure 4.6), and bring the solution to a gentle boil. As the reactants dissolve, evolution of nitrogen begins. Boil the blue solution for 1.5 hr to complete the reaction. Cool the solution to 50–60° and pour it into 10 mL of ice-water mixture, while stirring it. After crystallization of the benzil is complete, collect the crystals on a suction filter and wash them thoroughly with water. Press the product as dry as possible on the filter. The yield is 1.4–1.6 g (dry weight). Benzil obtained in this way is sufficiently pure for conversion to dilantin. If desired, it may be purified by recrystallization from methanol or 75% aqueous ethanol.

**Benzil \(\alpha\)-monoxime.** The benzil can be characterized by preparing the oxime derivative. In a test tube place 200 mg of benzil, 1 mL of ethanol, 0.2 mL of 35% aqueous solution of hydroxylamine hydrochloride, and 0.4 mL of 30% aqueous sodium hydroxide. Swirl the mixture and allow it to stand at room

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\(^1\) The catalyst solution may be prepared by dissolving 2.5 g of cupric acetate monohydrate in 100 mL of 10% aqueous acetic acid, stirring well, and filtering to remove any copper salts that have precipitated.
condensation of benzil with urea to form dilantin

48.4 Condensation of Benzil with Urea to Form Dilantin

Benzil and urea when heated together with base as catalyst condense to form dilantin. The process involves a skeletal rearrangement with both phenyls ending up on the same carbon atom. One possible sequence is shown here.

The first step involves base abstraction of an amide proton followed by addition to one of the carbonyl groups of benzil. Subsequent proton transfer and loss of water give the indicated condensation intermediate. This step is analogous to the aldol condensation discussed in Chapter 34. The second step starts off similar to the first, but after the addition to the carbonyl, the attached phenyl group migrates to produce the dilantin skeleton. Protonation then gives dilantin. The rearrangement is analogous to the benzilic acid rearrangement discussed in Chapter 35. It is not clear in this case why the rearrangement occurs. Perhaps it is the stability of the imide (—CO—NH—CO—) group that drives it.
**Dilantin.** In a small round-bottomed flask place 400 mg of unrecrystallized benzil, 200 mg of urea, 6.0 mL of ethanol, and 1.2 mL of 30% aqueous sodium hydroxide. Attach an upright condenser, add a boiling chip, and boil the mixture gently for 1 hr. Cool the reaction mixture, add 10 mL of water, and filter the solution to remove a sparingly soluble side product that sometimes forms. Acidify the filtrate with hydrochloric acid, collect the product on a suction filter, and wash it thoroughly with water. The product may be recrystallized from ethanol. The yield is 0.28–0.40 g. The recorded melting point is 286–295°C; do not attempt to determine the melting point with an oil bath (caution—dilantin is a powerful therapeutic agent and must be taken only on the advice and supervision of a physician!).

**Questions**

1. Draw the structure of the product formed by addition of vitamin B₁ and benzaldehyde.

2. Ammonia adds to carbonyl groups but it is ineffective as a catalyst for the benzoic condensation. Explain.

3. Write a balanced oxidation–reduction equation for the oxidation of benzoin by ammonium nitrate (the cupric ion catalysis need not be considered).

4. In the benzil oxidation the initial blue color changes to green as the reaction proceeds. Why?

5. In dilantin sodium it is the imide proton that is abstracted rather than the amide proton. Why?