Obtaining the Phenytoin and the Influence of Different Reaction Parameters

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Summary

Phenytoin is a very important drug in the treatment of epilepsy. This study prepared the phenytoin in the laboratory, with reagents and quality chemicals without further purification. The synthesis was used for condensation benzyl with urea, with solvents in the presence of various catalysts. This study was conducted to determine the optimum conditions to synthesize phenytoin, aiming to influence of various reaction parameters. To obtain the best of phenytoin was intended as catalysts influence and the influence of various reaction parameters.

Keywords: phenytoin, epilepsy treatment, antiepileptic drug.

Introduction

Phenytoin is an antiepileptic drug that can be used in the treatment of epilepsy. The main site of action appears to be the motor cortex where the spread of seizure activity is inhibited. [1] By promoting the flow of sodium in neurons, phenytoin tends to settle against hyperexcitability threshold caused by excessive stimulation, or changes in the environment capable of reducing the sodium in the membrane. Phenytoin reduces the maximal activity of seizures. [2, 3]

Phenytoin also is used to control arrhythmias (irregular heartbeat) to treat migraines, headaches and pain of the facial nerve. [4-6]

According to the current level of knowledge and therapeutic means, epilepsy medication order is missing or at least significantly reduce seizures and adequate quality of life, in terms of minimal side effects of antiepileptic drugs.
Treatment starts with minimal therapeutic dose and gradually increased until the therapeutic efficacy or maximum tolerated dose is recommended. This increase is achieved in plates, assessing the therapeutic efficacy of each row stable serum (table is estimated that achieve stable serum after the drug is given a time constant equal to 5 times the half-life of the drug).

In 1838, the German chemist, Justus Liebig reported the discovery of phenytoin, but its use as an anticonvulsant drug was reported much later, after 100 years.

Phenytoin (diphenylhydantoin) was synthesized by the German physician Heinrich Biltz in 1908. [7] In 1938, it was discovered the usefulness of phenytoin in controlling seizures without sedative effects associated with phenobarbital. There are some indications that phenytoin has other effects, including anxiety control and mood stabilization. [2]

Phenytoin, can also be used to control seizures occurring during neurosurgical problems [5]. For example, several applications have been reported as of hydantoin: antiarrhythmic and antihypertensive drugs [8], antiviral [9], antineoplastic [10], antitumor [11] and anticonvulsant [12, 13].

Antiepileptic drugs affect motor functions of the central nervous system (SNC).

Synthesis of CNS acting seem content with the purity could be achieved by omitting the solvent interference. Epilepsy is a common neurological condition that affects 0.5-1% of the population worldwide (45-10 million people) [14].

Synthesis of heterocycles becomes an important area of research in organic chemistry, the interest is not only for chemists, biochemists and biologists but also because of their presence in nature.

These compounds are known to participate in the metabolic pathway of living organisms and perform many biochemical functions, and are therefore widely used. The literature discloses that 60% of the pharmaceuticals used in treatment systems are heterocycles and 95% of these are N-functionalized [15-17].

Hydantoin nucleus is a 5-membered ring (of which three are carbon atoms), which contains a basic reactive cyclic urea. This heterocycle is present in a wide range of biologically active compounds, anti-arrhythmic agents, anti-tumor agents and anticonvulsants. [18] Among these agents, phenytoin is the most common drug treatment for epilepsy [19].

As a result of the growing interest of medicinal chemists frame hydantoin, have developed a number of methods for obtaining effective and rapid synthesis of phenytoin and related compounds using microwaves. [20-22].

The method of synthesis consists of phenytoin in the base-catalyzed condensation of benzyl [22]. Aqueous two-phase systems may be used KOH/n-BuOH and PEG 600. [23]

Solvent removal after synthesis is the most difficult thing. This increases the cost of the finished product. Therefore, there have been some attempts at synthesis of the
phenytoin from the condensation of benzyl urea in the presence of a base (30% NaOH), and water as solvent green [24, 25].

Synthesis of 5,5-diphenylhydantoin (phenytoin) is carried out by reacting benzyl, and urea in the presence of sodium hydroxide. The reaction takes place in the presence of other catalytic base such as sodium ethoxide.

The reaction takes place according to the scheme:

\[
\text{Benzyl} + \text{Urea} \rightarrow \text{Phenytoin}
\]

**Materials and Methods**

**Reagents and materials**

For the synthesis of phenytoin all reagents and chemicals used were of analytical reagent grade and were purchased from Sigma Aldrich. In this work were used: urea, benzyl, methanol purity analytical reagents and used as such without further purification. Sodium hydroxide and hydrochloric acid and other materials used are reagent grade and are used without special treatment.

**Summaries**

The reaction takes place in a round-bottom glass flask equipped with a reflux condenser, in which is inserted benzyl, urea, catalyst and solvent. There is refluxing the mixture for hours. Then, the mixture was poured into an ice bath, which led to the formation of a solid, which was filtered using a Buchner funnel. The filtrate is concentrated sulfuric acid was added to pH 5.5-6. To give a white precipitate which was filtered with suction, recrystallized from 95% ethanol and dried.
RESULTS AND DISCUSSION

Phenytoin has been synthesized by condensation of benzyl urea in the presence of a solvent, the catalyst used is sodium hydroxide, sodium methoxy, sodium ethoxide, sodium propioxidul. The study was conducted to determine the best conditions for the synthesis of phenytoin, watching the influence of various reaction parameters: ratio of reactants, catalysts used, the concentration of catalyst, solvents used and the reaction time.

The influence of the molar ratio of the reactants

First goal was to influence the variation of the molar ratio of reactants, in the synthesis of phenytoin, in the presence of a reaction solvent (methanol), in the presence of water compared to synthesis. Benzyl mole ratios of urea range from 1:1 to 1:5.

The reaction takes place at the boiling point of methanol, respectively at the boiling point of water. In methanol synthesis temperature varies between 66-68°C and in the water temperature varies between 95-98°C. The amount of solvent used throughout the synthesis is 40% by mass to the reaction mixture. Benzyl molar ratio of sodium hydroxide is 1:3. The reaction time is 2.5 hours.

Table I illustrates changes in the efficiency of the reaction for the synthesis of phenytoin, at different molar ratios benzyl urea, both in the presence of methanol as the reaction solvent as well as water.

Table I. Variation at different molar yield benzyl urea

<table>
<thead>
<tr>
<th>Nr.crt.</th>
<th>Molar ratio of reactants Benzyl:urea</th>
<th>Solvent</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>1:1</td>
<td>methanol</td>
<td>37.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>water</td>
<td>30.0</td>
</tr>
<tr>
<td>2.</td>
<td>1:1.5</td>
<td>methanol</td>
<td>60.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>water</td>
<td>58.5</td>
</tr>
<tr>
<td>3.</td>
<td>1:2</td>
<td>methanol</td>
<td>82.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>water</td>
<td>80.9</td>
</tr>
<tr>
<td>4.</td>
<td>1:5</td>
<td>methanol</td>
<td>74.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>water</td>
<td>70.7</td>
</tr>
</tbody>
</table>

The graphic (Figure 1) present the experimental results.

It is noted that the following chart in Figure 1 with increasing benzyl molar ratio: urea of 1:1 to 1:2, the yield of synthesis increases in both versions, both as a solvent with methanol as well as water. When the molar ratio of benzyl urea 1:1.5 yield decreases, we assume that secondary reactions occur.

Increasing the molar ratio of benzyl urea in the two versions work in methanol,
Obtaining the phenytoin and the influence of different reaction parameters

Water that determines values close enough reaction yields. This allows us to say that we successfully use water as a reaction solvent. Removal of the solvent reaction system is quite difficult, making water use more economical option. This can lead to lower cost price of the active substance phenytoin and thus lowering drug prices.

The influence of used catalysts

In the case of the synthesis of a phenytoin production rate of reaction is increased by addition of catalysts to the reaction.

Experimental have been used as catalysts in the synthesis reaction: sodium hydroxide, sodium ethoxide and sodium methoxide.

Benzyl molar ratio: catalyst of it 1:3.

The molar ratio of the reactants benzyl urea, is used in the synthesis of 1:2. The final reaction time was 2.5 hours.

The reaction takes place at the boiling point of methanol (66-68°C). The amount of solvent used throughout the synthesis is 40% by mass to the reaction mixture.

Table II presents the results obtained at different reaction catalysts used.

<table>
<thead>
<tr>
<th>Nr.crt.</th>
<th>Catalyst</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Sodium methoxide</td>
<td>88.5</td>
</tr>
<tr>
<td>2.</td>
<td>Sodium ethoxide</td>
<td>86.4</td>
</tr>
<tr>
<td>3.</td>
<td>Sodium hydroxide</td>
<td>82.1</td>
</tr>
</tbody>
</table>

The variation of the yield depending on the catalyst used is shown in the graph of Figure 2.

Figure 1. Variation at different molar yield of benzyl urea

Figure 2. The variation of the yield depending on the used catalyst
When using the three catalysts in the synthesis of phenytoin is observed that the best yields are obtained when working with sodium methoxide. And using two catalysts of others is possible, as are obtained in good yields (over 80%).

**The influence of the concentration of the catalyst**

We studied the influences of the concentration of sodium methoxide used for obtaining phenytoin. Phenytoin yields were monitored for reactions employing a molar ratio of benzyl urea of 1:2. The reaction temperature is the temperature of methanol distillation, or 65 -66°C.

The molar ratio of benzyl: sodium methoxide ranges from 1:1 to 1:3 in the condensation with urea benzyl. The amount of the solvent (methanol) is used throughout the synthesis to 40% by mass of the reaction mixture.

In Table III are shown the results obtained at various concentrations of sodium methoxide.

**Table III. Laboratory data obtained in the synthesis carried out with different concentrations of sodium methoxide**

<table>
<thead>
<tr>
<th>Nr.crt.</th>
<th>Benzyl: Catalyst</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>1 : 0.5</td>
<td>30.9</td>
</tr>
<tr>
<td>2.</td>
<td>1 : 1</td>
<td>60.2</td>
</tr>
<tr>
<td>3.</td>
<td>1 : 3</td>
<td>88.5</td>
</tr>
</tbody>
</table>

Yield values obtained at different concentrations of sodium methoxide are shown in Figure 3.

![Figure 3. The variation of yield with time depending on the concentration of the catalyst](image)

It consists of the graph in Figure 3 that with increasing benzyl molar ratio: catalyst increases the reaction rate of condensation of benzyl urea. Yield reaches 88.5% when using a mole ratio of benzyl:sodium methoxide 1:3.
The influence of reaction time

To follow the influence of reaction time on the yield variation phenytoin were conducted in laboratory syntheses from different reaction times. The molar ratio of benzyl urea was used in the synthesis of 1:2. The molar ratio of benzyl:sodium methoxide used is 1:3.

The reaction time is used during the refluxing of the reaction mixture. Were used to reflux for 30 minutes 150 minutes (2.5 hours), 5 hours, and the last version refluxing lasted for 5 hours.

Temperature range is between 66-68°C, the boiling point of methanol.

The experimental data are shown in Table IV.

Table IV. Variation in the reaction time to yield

<table>
<thead>
<tr>
<th>Nr.Crt.</th>
<th>Reaction time [min]</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>30</td>
<td>30.5</td>
</tr>
<tr>
<td>2.</td>
<td>150</td>
<td>88.5</td>
</tr>
<tr>
<td>3.</td>
<td>300</td>
<td>90.4</td>
</tr>
<tr>
<td>4.</td>
<td>400</td>
<td>91.8</td>
</tr>
</tbody>
</table>

The graph in Figure 4 are the results obtained in the laboratory synthesis of benzyl phenytoin and urea, using sodium methoxide as a catalyst for the reaction.

Figure 4. The variation of the yield depending on the reaction time

Following the graph in Figure 4 shows that the yield increases with reaction time, the best performance (91.8%) is obtained when using a reaction time of 400 minutes.

Low yield were obtained from the reaction of benzyl alcohol and urea in the presence of sodium methoxide, at a contact time of 30 minutes. After 150 min of reaction yield is good (88.5%), therefore it is desirable to use a reaction time of 150 minutes, further increasing efficiency is quite low.

Phenytoin crude processed and purified by recrystallization. Phenytoin purified dried at 70°C, and characterized the physico-chemical.
Phenytoin is obtained a white solid crystallized. It was noted that: phenyton slightly soluble in chloroform, sparingly soluble in alcohol and ether, practically insoluble in water mixing phenytoin and ammonia solution with a solution of CuSO₄ is observed precipitate a pink-purple.

Phenytoin is obtained having a melting point determined by 289-290° C. Is shown in Figure 5 IR spectrum of purified phenytoin.

![Figure 5. IR spectra of phenytoin obtained](image)

IR spectrum can observe some characteristic absorption bands of various important groups in the structure of phenytoin. Thus, peaks at 3266 cm⁻¹ (high intensity) and at 3208 cm⁻¹ corresponding to $\nu_{\text{N-H}}$ stretching vibration, and the vibration at 3074 cm⁻¹ stretch $\nu_{\text{C-H}}$ arom. There are high intensity peaks at 1738 and 1717 cm⁻¹ (i) which are attributable to the stretching vibration of C=O grouping, $\nu_{\text{C=O (ketone)}}$. Peaks appear at 1494 cm⁻¹ (w) attributable to the stretching vibrations $\nu_{\text{C-C}}$ aromatic 1482 and 1400 cm⁻¹, characteristic absorption bands $\delta_{\text{C-H}}$ bending vibrations. Symmetric stretching vibration band characteristic $\delta_{\text{C-N}}$ appears to 1324 (w) cm⁻¹. The spectrum peaks appear at 1288 cm⁻¹ (vi), 1195 cm⁻¹ (vi), 1155 cm⁻¹ (w) which are characteristic $\nu_{\text{C-C}}$ stretching vibration, that vibration characteristic stretching band-O $\nu_{\text{C}}$ 1117 (vi), 1071 (vi) and 1030 cm⁻¹ (w). In the 782.42 - 695.93 cm⁻¹ there are characteristic absorption bands $\delta_{\text{C=H}}$ bending vibrations (characteristic flavors) and monosubstituted phenyl ring vibrations.

**Conclusion**

1. In the study have established the optimal conditions for the synthesis of phenytoin by condensing benzyl urea, in the presence of alkaline catalysts. The syntheses were carried out in the presence of various reaction solvents (alcohols) but also in their absence. It was noted that if you quit working only in solvents and aqueous (water is considered solvent) can achieve good results. In the future we intend to establish and optimum conditions of synthesis of phenytoin in the absence of reaction
1. Optimal conditions determined for the synthesis involves the use of phenytoin-benzyl molar ratio: urea of 1:2 at a molar ratio of catalyst (sodium methoxide): benzyl 3:1. The solvent used is methanol and 40% by mass is used to the reaction mixture. The reaction temperature varies between 66 and 68°C, and the optimum synthesis time is 150 minutes.

2. Phenytoin has been synthesized and purified by recrystallization characterized by physico-chemical methods.

**References**

15. Park K.H., Ehrer J., Spoerri H., Kurth M.J., "Preparation of a 990-member chemical compound