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Study of Anticonvulsant Drug (Phenytoin) Along with Synthesis and Pharmacological Effect

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Abstract

Phenytoin is slowly but nearly completely absorbed in the small intestine; oral bioavailability ranges from 70 to 100%. The drug is widely distributed in the body and is almost completely protein-bound, primarily to albumin. Phenytoin is metabolized primarily in the liver by CYP2C9 and CYP2C19 to 5-(4-hydroxyphenyl)-5-phenylhydantoin, which is glucuronidated and excreted. Minor metabolites that are produced include 3,4-dihydrodiol, catechol (3,4-dihyroxyphenyl-phenylhydantoin), and 3-*O*-methylated catechol. Since hepatic metabolism is a saturable process, small increases in dosage can result in very large increases in serum levels. CYP2C9 also metabolizes warfarin and tolbutamide, which may explain interactions between phenytoin and these drugs. Phenytoin and metabolites may undergo enterohepatic recirculation prior to excretion. Most of the drug is eliminated in the urine as inactive conjugated metabolites, but small amounts of the unchanged drug may be present in the urine (2–4%) and feces (5%). In this study we prepared Phenytoin from Benzil and urea and determined it percentage yield.

Keywords: Phenytoin, Benzil, Urea, Percentage yield

Introduction

Phenytoin is used to control certain type of seizures, and to treat and prevent seizures that may begin during or after surgery to the brain or nervous system. It is in a class of medications called anticonvulsants. It works by decreasing abnormal electrical activity in the brain. It has not only been established as an effective anti-epileptic, but has also been investigated for several other indications such as bipolar disorder, retina protection, and wound healing. Phenytoin was first made in 1908 by the German Chemist Heinrich Biltz and found useful for seizures in 1936 [1, 2].

Epilepsy is a central nervous system (neurological) disorder in which brain activity becomes abnormal, causing seizures or periods of unusual behavior, sensations and sometimes loss of awareness. Epilepsy affects both males and females of all races, ethnic backgrounds and ages [3].

Symptoms: A staring spell, temporary confusion, stiff muscles, uncontrollable jerking movements of the arms and legs, loss of consciousness or awareness, psychological symptoms such as fear, anxiety or déjà vu, seizure. A seizure is a burst of uncontrolled electrical activity between brain cells (also called neurons or nerve cells) that cause temporary abnormalities in muscle tone or movements (stiffness, twitching or limpness), behaviors, sensations or states of awareness [4].

Material and Method

Chemicals: - Benzil, urea, sodium hydroxide, ethanol, HCl

Apparatus:- Round-bottom flask- 100 ml , reflux condenser , crystallizing disk- 500 ml , heating mantle , stirrer , beaker- 400 ml , funnel , graduated cylinder – 100 ml , Petri dish , whatman filter paper and butter paper etc.

Preparation of Phenytoin from Benzil and Urea

Principle

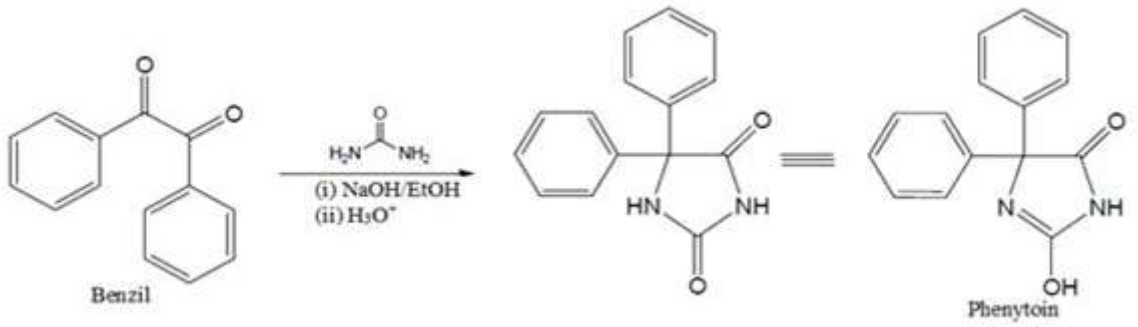
Base catalyzed reaction between benzyl and urea is used for synthesis of phenytoin. The reaction is pro intramolecular cyclization to form an intermediate heterocylic pinacol, which on acidification yield hydantoin a result of 1,2-diphenyl shift in pinacol rearrangement reaction.

Procedure

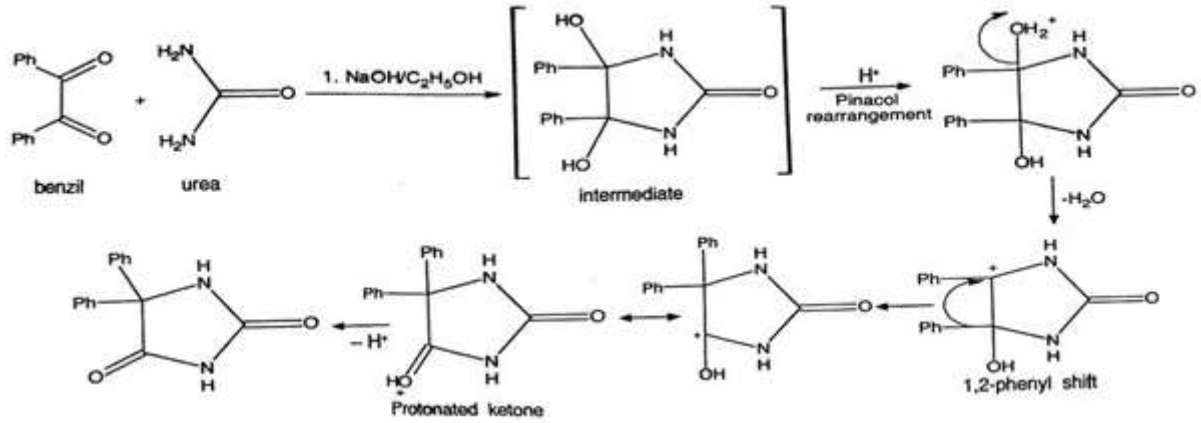
Place 5.3 g (0.025 mol) of benzil, 3.0 g (0.05 mol) of urea, 15 ml of aqueous sodium hydroxide solution (30%) and 75 ml of ethanol in a round bottomed flask of 100 ml capacity, and then Set up a reflux condenser with the flask and boil using an electric heating mantle for at least 2 hrs and Cool it at room temperature after that pour the reaction mixture into 125 ml of water and mix carefully and Allow the reaction mixture to stand for 15 min And then filter the product under suction to

remove an insoluble by-product and then give the filtrate strongly acidic with concentrated hydrochloric acid, And then cool in ice-water after that immediately filter off the precipitated product under suction. Recrystallized at least once from hydrochloric acid to obtain about 2.8 g (44%) of pure 5, 5-diphenylhydantoin, Melting Point-297-298°C [5, 6].

Reaction



Mechanism



Calculation

Molecular Weight of Benzil = 210.23 gm/M

Molecular Weight Phenytoin = 252.26 gm/M

Weight Taken of Benzil = 5 gm

Practical Yield= 5.6 gm

Theoretical Yield = Molecular Weight Of Phenytoin × Weight Of Benzil taken

Molecular Weight of Benzil

= 252.26 gm/M × 5gm = 5.9 gm

210.23gm/M

Percentage Yield = Practical Yield / Theoretical Yield × 100 %

Percentage Yield = 5.6 gm / 5.9 gm × 100%

Percentage Yield = 94.9%

Pharmacology of Phenytoin

Mechanism of action

Phenytoin is believed to protect against seizures by causing voltage-dependent block of voltage gated sodium channels. This blocks sustained high frequency repetitive firing of action potentials. This is accomplished by reducing the amplitude of sodium-dependent action potentials through enhancing steady-state inactivation. Sodium channels exist in three main conformations: the resting state, the open state, and the inactive state. Phenytoin binds preferentially to the inactive form of the sodium channel. Because it takes time for the bound drug to dissociate from the inactive channel, there is a time-dependent block of the channel. Since the fraction of inactive channels is increased by membrane depolarization as well as by repetitive firing, the binding to the inactive state by phenytoin sodium can produce voltage-dependent, use-dependent and time-dependent block of sodium-dependent action potentials [7].

The primary site of action appears to be the motor cortex where spread of seizure activity is inhibited. Possibly by promoting sodium efflux from neurons, phenytoin tends to stabilize the threshold against hyperexcitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient. This includes the reduction of post-tetanic potentiation at synapses which prevents cortical seizure foci from detonating adjacent cortical areas. Phenytoin reduces the maximal activity of brain stem centers responsible for the tonic phase of generalized tonic-clonic seizures [8].

Result

The Phenytoin was prepared using benzil and urea and its yield is found to be 94.9%. Its maximum solubility is found to be in aqueous media. The pharmacological action of Phenytoin is to protect against seizures by causing voltage-dependent block of voltage gated sodium channels which blocks sustained high frequency repetitive firing of action potentials. This is accomplished by reducing the amplitude of sodium-dependent action potentials through enhancing steady-state inactivation.

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