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Synthesis of 5,5-Diphenyl-2,4-imidazolidinedione (Phenytoin) from Almond

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In present studies, it is proposed to synthesized phenytoin from the easily accessible starting materials which are available in Iran. Almond kernels were ground then, through steam distillation and extraction methods, almond oil and subsequently benzaldehyde were isolated and purified. Benzaldehyde under the influence of sodium cyanide in aqueous alcohol undergone a dimolecular condensation reaction and gave benzoin. Oxidation of benzoin with concentrated nitric acid yielded benzil. Benzil on treatment with urea in alcoholic solution in presence of NaOH (30 %) first gave benzilic acid, then through a condensation reaction with urea and after acidification of the filtrate with HCl (2 M) gave 5,5-diphenyl-2,4-imidazoli-dinedione (Phenytoin). The chemical structures of the intermediates and products were determined through their IR, ^{1}H NMR and MS (EI) spectra.

Key Words: Phenytoin, 5,5-Diphenyl-2,4-imidazolidinedione, Benzil, Benzaldehyde, Benzoin.

INTRODUCTION

Phenytoin sodium is a commonly used antiepileptic. Phenytoin is used to treat various types of convulsions and seizures, acts on the brain and nervous system in the treatment of epilepsy and to damp the unwanted, runaway brain activity seen in seizure by reducing electrical conductance among brain cells by stabilizing the inactive state of voltage gated sodium channels. Phenytoin is also used to control arrhythmias (irregular heartbeat) and to treat migraine headaches and facial nerve pain. Phenytoin (diphenylhydantoin) was first synthesized by German physician Heinrich Biltz in 1908. In 1938, outside scientists including H. Houston Merritt and Tracy Putnam discovered phenytoin's usefulness for controlling seizures, without the sedative effects associated with phenobarbital. There are some indications that phenytoin has other effects, including anxiety control and mood stabilization[1]. Phenytoin

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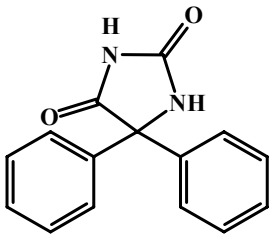
(**VI**), in the form of its sodium salt, can be formulated into a propylene glycol-alcohol-water solution that is used for parenteral administration. Phenytoin is the antiepileptic of choice for most patients with tonic-clonic status epilepticus of the grand mal type with focal and psychomotor seizures[2]. Phenytoin can also be used to control seizures occurring during neurosurgery when given at 100-200 mg intramuscularly at 4 h intervals.



(**VI**) 5,5-diphenylimidazolidine-2,4-dione; $C_{15}H_{12}N_2O_2$, m.w. = 252.268 g/mol

EXPERIMENTAL

All reagents and chemicals were of analytical reagent grade and were purchased from Merck and Pars Iran Chemical Companies. They were used without further purification for the preparation and synthesis of the intermediates and products. Dried bitter almonds were purchased the markets in Ahwaz, Iran.

All intermediates and products were routinely examined by proton NMR (Bruker, Germany, 300 MHz), IR (JASCO, 700 IR) and mass spectrometer (Finnigan MAT: Q70, USA).

Preparation of benzaldehyde from bitter almond: First, the kernels were separated crushing the dried fruit, then, they were powdered by an electrical mill. The powdered kernels were poured inside a metallic vessel and placed under a hydraulic press and pressure was exerted until its fatty oil was extracted. The residue was crushed again and macerated in warm water (40-60 °C) for 24 h. During this time, glycosidic amygdalin was hydrolyzed and the volatile oil (almond oil) was isolated. Steam distillation of the mixture resulted in the separation of the volatile oil along with hydrocyanic acid (HCN). In order to separate the acid, calcium hydroxide solution was added to the mixture and distilled, benzaldehyde was separated, the yield was low (*ca.* 0.4 %) and the whole process was repeated several times. The IR spectrum (neat liquid) of benzaldehyde had ν_{max} (cm^{-1}): 2840, 2730 (CH, aldehyde, m-w), 1694 (C=O, s), 1597, 1583, 1454 (C=C, aromatic ring, m).

Preparation of benzoin from benzaldehyde: In a 1000 mL round-bottomed flask, ethanol (200 mL 95 %), benzaldehyde (150 g, 142.5 mL, 1.41 mol) and a solution of sodium cyanide (15 g) in water (150) were placed and refluxed for 3 h. Then, the contents of the flask were cooled in an ice bath. Benzoin was precipitated as a solid material and collected over a Buchner funnel. It was washed several

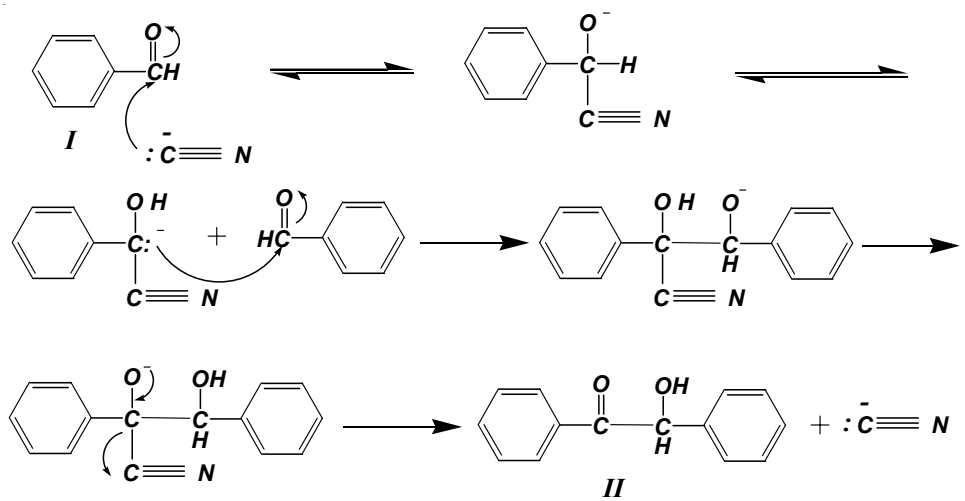
times with cold distilled water to remove the excess sodium cyanide. A second batch of benzoin was obtained by heating the mother liquor on a hot plate. The batches were added together and recrystallized from 95 % ethanol. Pure benzoin was obtained as a white crystalline material (130 g, 0.511 mol, 87 %). Its m.p. was found to be 128-130 ºC (literature 134-135 °C)[3]. Its IR (mull in nujol) ν_{max} (cm^{-1}): 3500-3100 (OH, br, s), 3050 (C=CH, aromatic), 1680 (C=O, s), 1590, 1585, 1480 (C=C aromatic, m); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 4.85 (s, 1×H, OH), 5.95 (s, 1×H, CH), 7.36, 7.96 (5×H aromatic ring), 7.36-7.42 (t, 2×H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 133.4 (C1 of ring A), 138.9 (C of ring B), 133.8, 129.1, 128.6, 128.5, 127.7 (10×C atoms of rings A and B), 198.9 (C=O); MS (EI) showed m/z: 212 {$[M]^+$, 6 %}, 195 {$[M\text{-}OH]^+$, 58 %}, 105 {$[M\text{-}PhCHOH]^+$, 100 %}, 77 {$[M\text{-}(PhCHOH + CO)]^+$, 33 %}.

Preparation of benzil from benzoin: Benzoin (50 g, 0.235 mol) was placed in a 1000 mL Erlenmeyer flask and concentrated nitric acid (250 mL) was added into it in a fume cupboard. The mixture was heated on a hot plate with occasional shaking until all the red coloured nitrogen oxide gas was evolved (*ca.* 2 h). The mixture was transferred to another 2000 mL Erlenmeyer flask which contained 1000 mL distilled water and stirred vigorously until the oil solidified as a yellow crystalline material. It was filtered over a Buchner funnel and washed with a liberal quantity of cold water until all the excess HNO_3 was removed. The solid material was recrystallized from 95 % ethanol which resulted yellow needle crystalline material (44 g, 0.21 mol, 89 %). Its m.p. was found to be 92 °C (literature 95 °C)[3]. IR (mull in nujol) ν_{max} (cm^{-1}): 3050 (C=CH, aromatic), 1680 (C=O, s), 1595, 1585, 1450 (C=C aromatic, m); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.48-7.54 (t, 2×H aromatic ring), 7.54-7.58 (t, 1×H), 7.96-7.98 (t, 2×H aromatic ring); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 129.8 (C3, C3'/C2, C'), 129.8 (C2, C2'/C3, C3'), 132.9 (C1, C1'), 134.8 (C4, C4'), 194.5 (C=O); MS (EI) showed m/z: 210 {$[M]^+$, 17 %}, 105 {$[M\text{-}PhCO]^+$, 100 %}, 77 {$[M\text{-}(PhCHOH + CO)]^+$, 16 %}.

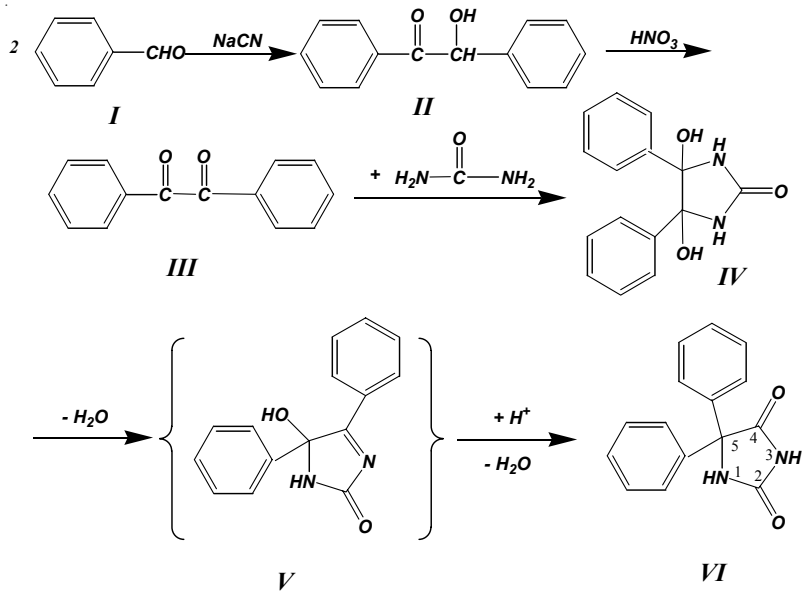
Preparation of phenytoin: In a 1000 mL round-bottomed flask which contained 200 mL absolute ethanol and equipped with a reflux condenser, benzil (8.8 g, 0.042 mol), urea (4.38 g, 0.073 mol) and sodium hydroxide pellets (4.7 g, 0.084 mol) were placed and refluxed for 8 h. Then, the mixture was poured in an ice bath which resulted in the formation of a solid material which was filtered over a Buchner funnel. To the filtrate, concentrated sulphuric acid was added until the pH became 5.5-6.0 and a white solid material was obtained. It was collected over a Buchner funnel and recrystallized from 95 % ethanol; a white crystalline material was obtained (6 g, 0.024 mol, 60 %). Its m.p. was found to be 288-291 °C (literature 293 °C)[4]. Its IR (mull in nujol) ν (cm^{-1}): 3050 (C=CH, aromatic), 1719 (C=O, s), 1520, 1480, 1440 (C=C aromatic, m); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.64 (NH), 7.26-7.52 (m, 10×H aromatic ring), 10.22 (s, 1×H, OH enol); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 125.7-135.17 (12×C atoms of aromatic rings), 156.2 (C=O); MS (EI) showed m/z: 242{$[M]^+$, 17 %}, 237 {$[M\text{-}NH]^+$, 100 %}, 180 {$[M\text{-}(Ph)_2C{=}N]^+$, 40 %}, 77 {$[C_6H_5$, 20 %}.

RESULTS AND DISCUSSION

An interesting and useful synthesis of hydantoins is the condensation of α-diketones or α-dialdehydes with urea, followed by a pinacolone rearrangement. In the presence of cyanide ion, benzaldehyde (**I**) undergoes benzoin condensation, yielding benzoin (**II**) (**Scheme-I**). The formation of the hydantoin (**VI**) (**Scheme-II**), involves a molecular rearrangement in which a phenyl group undergoes a 1,2-shift and has been cited as an example of the pinacol rearrangement[5,6]. It is accepted that the reaction proceeds stepwise with the formation of the intermediate 4,5-diphenyl-4,5-dihydroxy-2-imidazolone (**IV**) followed by a pinacol rearrangement to the hydantoin (**VI**)[7]. The reaction is carried out in 95 % aqueous ethanol and the product, which is sparingly soluble, crystallizes from the reaction mixture on cooling. The product was collected by vacuum filtration and recrystallized from 95 % ethanol. On the other hand, benzaldehye (**I**) was isolated from almond oil which in turn was obtained by steam distillation from the dried ripe kernels of *Prunus amygdalus* (it can also be obtained from other kernels containing amygdalin such as apricots and peaches). Before distillation, the kernels were freed of their fatty oil by expression and the powdered, pressed cake was macerated in warm water to hydrolyze the glycoside, amygdalin. The yield from bitter almonds was about 0.4-0.6 %. The main constituent was benzaldehyde (*ca.* 90 %). The chemical structures of all the intermediates and products were elucidated and determined through their IR, ^{1}H NMR, ^{13}C NMR and MS (EI) spectra.



Scheme-I



Scheme-II

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