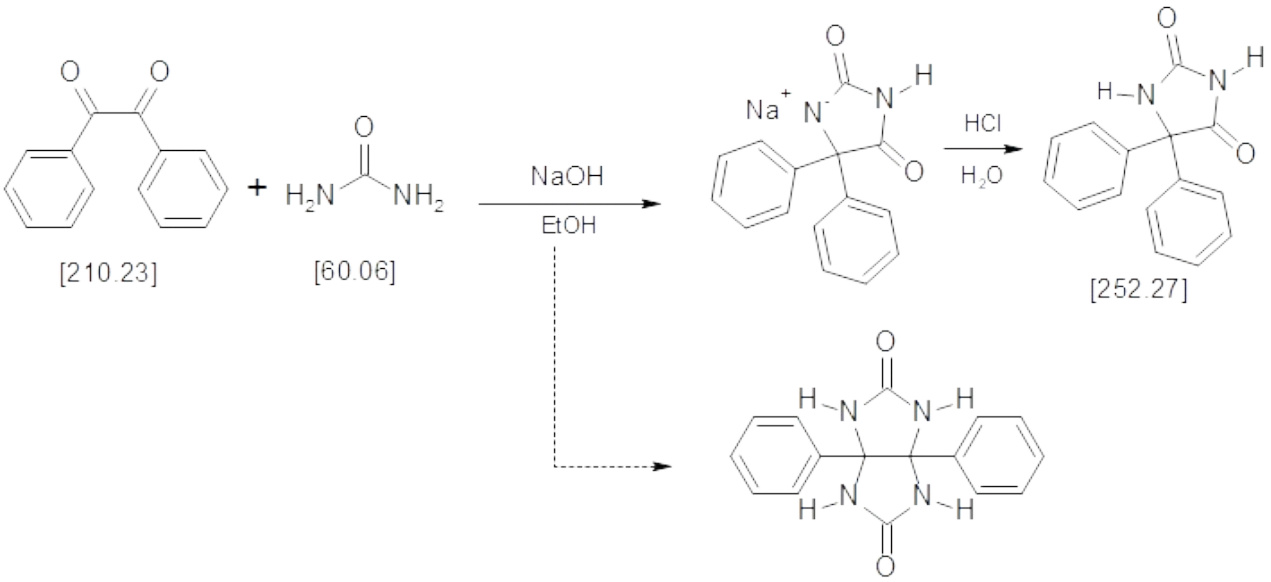
4. Phenytoin

Systematic name: 5,5-diphenylimidazolidine-2,4-dion; 5,5-diphenylhydantoine

Chemicals:

benzil (1,2-diphenylethan-1,2-dione)	[210.23]	0.0095 mol
urea	[60.06]	0.017 mol
sodium hydroxide	[40.0]	0.045 mol
Ethanol 96%		30 ml
Distlilled water		6 ml
Hydrochloric acid 35%		q.s.

Scheme of preparation:



Procedure:

Benzil is dissolved in 30 ml of ethanol in a 14 mm-necked rounded-bottom flask. Then, water and sodium hydroxide are added and stirred by a circular movement until NaOH is dissolved. Finally, urea and a stirrer bar are added. The reaction mixture is then refluxed under stirring on a magnetic stirrer for 2 hours. After finish of heating, the flask is let to cool down and then 40 ml of water are added, and the flask is placed into an ice bath. After cooling down, the side product of the reaction, diphenylglycoluril, is formed as a precipitate. It is isolated by suction. The filtrate is then poured into a beaker and made acidic by adding of hydrochloric acid *(check with an indicator paper !)*. A white precipitate of the product is being formed simultaneously with adding of the acid. The precipitate is isolated by suction and washed well on the filter with plenty of water. Then it is recrystallized from ethanol with addition of activated charcoal.

Recrystallization procedure: The product is given back to the flask and minimal needed volume of ethanol (up to 50 ml) and a pinch of the activated charcoal are added. The mixture is then heated until boiling. If the product is not completely dissolved, a volume of ethanol just needed for its complete dissolving is added. Then, the mixture is quickly filtered through a folded filter placed in a preheated funnel into a beaker. The beaker is then cooled down in an ice bath and crystalline material is being formed. Crystals are isolated by suction and let to dry on a Petri dish.

Purity of the product, especially the absence of starting benzil, is then tested by TLC with benzil as the comparison compound. After drying to the next practical lesson, the identity of the product is confirmed by ^{1}H- and ^{13}C-nuclear magnetic resonance (NMR) spectroscopy: place approx. 20 mg of the dried substance into a plastic tube with a lid („Eppendorf tube“) and consult your lecturer.

Properties:
Phenytoin is a colourless micro-crystalline compound of m.p. 293-296°C, insoluble in water, benzene and chloroform. (The side reaction product 1,5-diphenyl-2,4,6,8-tetraazabicyclo[3,3,0]octan-3,7-dione or 3a,6a-diphenyltetrahydroimidazo[4,5-*d*]imidazole-2,5-(1*H*,3*H*)-dione, or diphenylglycoluril has m.p. 390 – 394°C. Both melting temperatures are, unfortunately, not measurable on a common capillary melting point apparatus.) Phenytoin dissolves in alkaline hydroxides solutions forming salts. It was first prepared by Biltz and Rimpel as early as in 1908. It is still used as an antiepileptic (Epilan D Gerot®).