2. Lidocaine

Systematic names: 2-diethylamino-*N*-(2,6-dimethylphenyl)acetamide, 2´,6´-dimethyl-2-diethylaminoacetanilide

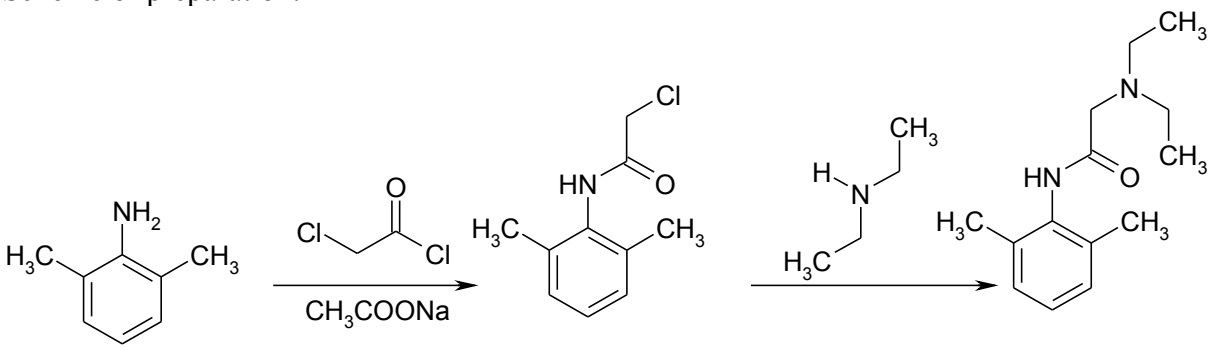
Synthesis of this compound uses 2,6-dimethylaniline (2,6-xylidine) as the starting material. 2,6-xylidine is transformed by chloroacetylchloride in acetic acid at presence of sodium acetate into 2-chloro-*N*-(2,6-dimethylphenyl)acetamide. The alkylation reaction of 2-chloro-*N*-(2,6-dimethylphenyl)acetamide with diethylamine gives desirable 2-diethylamino-*N*-(2,6-dimethylphenyl)acetamide (lidocaine) which is then transformed by ethereal solution of hydrogen chloride into its salt well soluble in water (hydrochloride).

The reaction procedure thus consists of two steps:

1. **Preparation of 2-chloro-*N*-(2,6-dimethylphenyl)acetamide as an intermediate**
2. **Preparation of 2-diethylamino-*N*-(2,6-dimethylphenyl)acetamide (lidocaine)**

Due to lack of time both steps are performed <u>simultaneously</u>. At first start the refluxing of 2-chloro-*N*-(2,6-dimethylphenyl)acetamide in toluene (step 2) on the laboratory table. You will get the appropriate amount of intermediate from the pair which has done it last time or from a reserve. Then you will immediately start the chloroacetylation of 2,6-xylidine (step 1) at a magnetic stirrer in a fume cupboard.

Scheme of preparation:



Procedure
Step 1: 2-chloro-N-(2,6-dimethylphenyl)acetamide (or chloroaceto-2,6-xylidide)

Chemicals:
2,6-dimethylaniline (2.6-xylidine) 0.05 mol
chloroacetyl chloride 0.06 mol
(*Calculate and measure **volumes** of both liquids; molecular weight and density data can be found on bottle labels, if not, see a laboratory chemicals catalogue. Ask a lecturer for checking of your calculated volumes before you start the preparation.)*
concentrated acetic acid 45 ml
sodium acetate 15g

The synthesis must be performed in a **fume cupboard**, both liquid and vapours of chloroacetyl chloride are harmful**.** Use a magnetic stirrer with a suitable stirrer bar. 2,6-Xylidine (0.05 mol) and 45 ml of concentrated acetic acid is mixed in an Erlenmayer flask and the solution is cooled down to 10°C in an ice bath. At this temperature, chloroacetyl chloride (0.06 mol) is slowly added under

continuous stirring. After the additional 30 min of stirring, the solution of 15 g of sodium acetate in 75 ml of water is added. A precipitate of 2-chloro-*N*-(2,6-dimethylphenyl)acetamide (= chloroaceto-2,6-xylidide) is formed. The reaction mixture is stirred one additional hour and then the precipitate is isolated by suction and washed with water on the filter. It must be dried enough before use in Step 2. In case of need it can be recrystallized from aqueous ethanol. Yield you should gain: 85-90 % of theory.

Properties: 2-chloro-*N*-(2,6-dimethylphenyl)acetamide is colorless or yellowish crystalline solid of m.p.t. 142°C (*should be measured at a capillary melting point apparatus*).

Step 2: 2-diethylamino-*N*-(2,6-dimethylphenyl)acetamide (lidocaine)

Chemicals:
chloroaceto-2,6-xylidide 0.03 mol
diethylamine 0.09 mol
hydrogen chloride ethereal solution q.s.
(*Calculate and measure **volume** of diethylamine and **weight** of chloroaceto-2,6-xylidide. Ask a lecturer for checking of your calculated amounts before you start the preparation and also for checking of functionality of your apparatus.*)
toluene 150 ml

2-chloro-*N*-(2,6-dimethylphenyl)acetamide (0.03 mol) is suspended in 150 ml of toluene in a round bottom 250 ml flask equipped with a condenser. Diethylamine (0.09 mol) is added. The reaction mixture is refluxed for 4 hours. After cooling, precipitated diethylammonium chloride is filtered off. The filtrate is extracted three times with 30 ml of water in a separatory funnel and, after separation of the third portion of water, dried with anhydrous sodium sulfate in a stoppered flat-bottom flask. The most of toluene is distilled off at a vacuum rotary evaporator. The residuum is poured into a suitable beaker and a small portion of ethereal hydrogen chloride is added. The mixture is vigorously stirred with a glass rod. At first, a matter similar to chewing gum is formed. Further intensive stirring and adding of additional portions of ethereal hydrogen chloride gradually lead to its disintegration. The yielded crystalline powder is isolated by suction on a glass filter, washed with pure diethyl ether, dried air-stream suction on the glass filter and finely dried at 70°C. Yield is usually approx. 70 % of theory. Identity of the prepared lidocaine hydrochloride is confirmed by **IR spectrum** (*The measurement is performed usually for several pairs together at the appropriate laboratory of the Department of natural drugs, consult the lecturer.*) and by **melting point** determination. Purity or, more accurately, absence of the intermediate 2-chloro-*N*-(2,6-dimethylphenyl)acetamide is confirmed by **thin layer chromatography (TLC)** on a silica gel plate. *Consult your lecturer for a suitable mobile phase.*

Properties:
Anhydrous lidocainium chloride forms colourless needle-shaped crystals of m.p. 128-129°C, its monohydrate melts at 78-79°C, both are very soluble in water, freely in ethanol and slightly in organic solvents.

Usage:
Lidocaine is official in the European Pharmacopoeia as both free base (Lidocaine – *Lidocainum*) and hydrochloride monohydrate (Lidocaine hydrochloride – *Lidocaini hydrochloridum*). It is widely spread local anaesthetic of anilide type used in both superficial and infiltration anaesthesia. Lidocaine has also antidysrhythmic properties; acts as a sodium channel inhibitor.