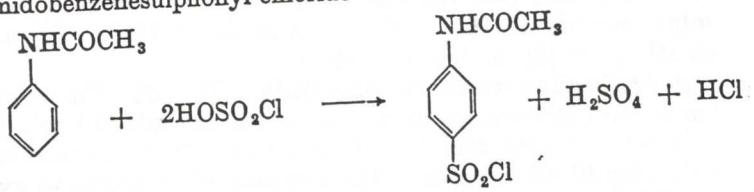
Référence : Vogel's Practical Organic Chemistry 3° ed p 1005

Sulfamides antibacteriens

IX,9. *p*-AMINOBENZENESULPHONAMIDE (SULPHANILAMIDE)

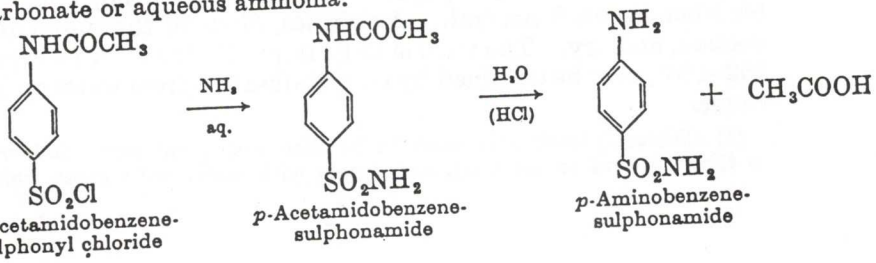
The synthesis of this important compound may be accomplished by the following series of reactions :

(i) Treatment of acetanilide with excess of chlorosulphonic acid affords *p*-acetamidobenzenesulphonyl chloride—a solid, m.p. 149° :

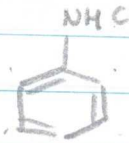


(ii) This is converted by aqueous ammonia into *p*-acetamidobenzenesulphonamide—the pure compound has m.p. 218°.

(iii) By boiling with dilute hydrochloric acid the protecting acetyl group is removed without hydrolysing the sulphonamido group. The liberated sulphonamide passes into solution as the hydrochloride, and the free base (*p*-aminobenzenesulphonamide) is obtained by neutralisation with sodium bicarbonate or aqueous ammonia.



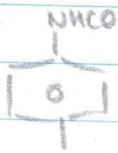
p-Acetamidobenzenesulphonyl chloride — *p*-Acetamidobenzenesulphonamide — *p*-Aminobenzenesulphonamide



2g $\quad n = \frac{2,0}{8 \times 12 + 16 + 17 + 9} = 0,15 \text{ mol}$

p-Acetamidobenzene sulphonyl chloride

$C_{NH_3} = 13,33 \text{ mol.L}^{-1}$



6,22 équivalents

$M = 135 + 32 + 16 \times 2 + 35,5$

$M = 234,5$

$m = 3g \quad n = 1,27 \times 10^{-2} \text{ mol} \quad \Rightarrow 6,22 \text{ éq}$

$n_{NH_3} = 7,9 \times 10^{-2} \text{ mol}$

$V = \frac{n}{C} = 5,93 \text{ mL}$

p-Acetamidobenzenesulphonyl chloride. Equip a 500 ml. bolt-head flask with a two-holed cork carrying a dropping funnel and a reflux condenser: attach the top of the latter to a device for the absorption of hydrogen chloride (*e.g.*, Fig. *II*, *8*, 1, *c*). Place 20 g. of dry acetanilide in the flask and 50 ml. (90 g.) of a good grade of chlorosulphonic acid {*CAUTION*: (1)} in the dropping funnel and insert a calcium chloride guard tube into the latter. Add the chlorosulphonic acid in small portions and shake the flask from time to time to ensure thorough mixing (2). When the addition has been made, heat the reaction mixture on a water bath for 1 hour in order to complete the reaction. Allow to cool and pour the oily mixture in a thin stream with stirring into 300 g. of crushed ice (or ice water) contained in a 1 litre beaker. Carry out this operation carefully in the fume cupboard since the excess of chlorosulphonic acid reacts vigorously with the water. Rinse the flask with a little ice water and add the rinsings to the contents of the beaker. Break up any lumps of solid material and stir the mixture for several minutes in order to obtain an even suspension of the granular white solid. Filter off the *p*-acetamidobenzenesulphonyl chloride at the pump and wash it with a little cold water; press and drain well. *Use the crude product* (3) *immediately in the next stage.*

p-Acetamidobenzenesulphonamide. Transfer the crude *p*-acetamidobenzenesulphonyl chloride to the rinsed reaction flask, and add a mixture of 70 ml. of concentrated ammonia solution (sp. gr. 0·88) and 70 ml. of water. Mix the contents of the flask thoroughly, and heat the mixture with occasional swirling (*FUME CUPBOARD*) to just below the boiling point for about 15 minutes. The sulphonyl chloride will be converted into a pasty suspension of the corresponding sulphonamide. Cool the suspension in ice, and then add dilute sulphuric acid until the mixture is just acid to Congo red paper. Collect the product on a Buchner funnel, wash with a little cold water, and drain as completely as possible. It is desirable, but not essential, to dry the crude *p*-acetamidobenzenesulphonamide at 100°: the yield is about 18 g. The material is sufficiently pure (4) for the next stage.

p-Aminobenzenesulphonamide. Transfer the crude *p*-acetamidobenzenesulphonamide to a 500 ml. flask, add 10 ml. of concentrated hydrochloric acid and 30 ml. of water. Boil the mixture gently under reflux for 30–45 minutes. The solution, when cooled to room temperature should deposit no solid amide; if a solid separates, heat for a further short period. Treat the cooled solution with 2 g. of decolourising carbon, heat the mixture to boiling, and filter with suction through a hardened filter paper. Place the filtrate (a solution of sulphanilamide hydrochloride) in a litre beaker and cautiously add 16 g. of solid sodium bicarbonate in portions with stirring. After the evolution of gas has subsided, test the suspension with litmus paper and if it is still acid, add more sodium bicarbonate until neutral. Cool in ice, filter off the sulphanilamide with suction, and dry. The yield is 15 g., m.p. 161–163°. A pure product, m.p. 163–164°, may be obtained by recrystallisation from water or from alcohol.

Notes.

(1) *Chlorosulphonic acid* must be handled with great care: it is very corrosive to the skin and to clothing, and reacts with water with great violence. If the