

ALIEN PROPERTY CUSTODIAN

PROCESS FOR THE PRODUCTION OF NEW EFFICACIOUS P-AMINO-BENZENE-SULPHAMIDE DERIVATIVES, SUITABLE FOR INJECTION PURPOSES

Zoltán Földi, Budapest, Hungary; vested in the Alien Property Custodian

Application filed February 5, 1938

Chemical compounds of the amino-benzene-sulphamide type are extensively used in the therapy, particularly for diseases due to streptococcal infection. However, p-amino-benzene-sulphamide is only to a very slight extent soluble in water and it is therefore unsuitable for preparing solutions of the necessary concentration. Neither are the salts formed by the said compounds with acids, suitable for preparing solutions intended for injection, because their aqueous solutions possess a strong acid effect.

According to our present invention it is possible to obtain p-amino-benzene-sulphamide derivatives readily soluble in water and suitable for injection purposes, if p-amino-benzene-sulphamide, or such derivatives of the same as result from substitutions effected in the nucleus or in the nitrogen atoms are subjected to the action of formaldehyde sulphonylate.

It has been found to be particularly advantageous to perform the reaction of the formaldehyde sulphonylate in the presence of about 1 mol of alkali metal hydroxide, in which case products, extremely soluble in water, are formed, which can be easily isolated from the reaction mixture by addition of mineral acid, whereupon an acid difficultly soluble in water will separate. If this acid is filtered off, washed with water and then neutralized by means of alkali metal hydroxides, as for instance, by sodium hydroxide, an aqueous solution of the product results in which product practically two atoms of sulphur correspond to two atoms of nitrogen i. e. in which product 1 mol of amino-benzene-sulphamide is connected with 1 mol of formaldehyde sulphonylate. Thus for instance 50 grams of p-amino-benzene-sulphamide are dissolved in a mixture of 70 ccm of water and of 20 to 25 ccm of a 47 per cent by volume sodium hydroxide solution by heating in a water-bath, and after cooling a solution of 50 to 100 grams of formaldehyde sodium-sulphonylate in 100 to 200 ccm of water is added. This mixture is heated at a temperature of 60 to 80° C during one hour, then the solution is cooled and to the filtered solution hydrochloric acid is added until a filtered test portion will not produce any further precipitate on the addition of hydrochloric acid. The precipitate is collected on a suction funnel, preferably excluding from air, and washed with water. The wet acid gives, neutralised with a solution of sodium hydroxide, a solution of the sodium salt which is easily soluble in water. It is, however, also possible to dry the acid in *vacuo* over phosphorus pentoxide and to effect the formation of the salt in an alcoholic medium.

If no sodium hydroxide is employed during the action of the sulphonylate, only a very slow reaction will take place between the sulphonylate and the amino-benzene-sulphamides (amino-benzene-sulphamide, benzylamino-benzene-sulphamide, amino-benzene-disulphamide etc.) In this case it will be preferable to employ the sulphonylate in a large excess e. g. two mols of sulphonylate per mol of amino-benzene-sulphamide. Such a reaction mixture has an alkaline reaction, owing to the hydrolysis of the excess of sulphonylate. In this case the heating of the reaction mixture (50 grams of p-amino-benzene-sulphonylate, 75 grams of formaldehyde sodium sulphonylate, free from water of crystallisation, and 100 ccm. of water) should be continued in a water bath of 70 to 90° C. during about 20 hours. The product formed during this process is likewise most easily soluble in water, but when acidified with mineral acids no free acid will precipitate. The isolation of the product from this reaction mixture is preferably effected by pouring it into a quantity of absolute alcohol amounting to between 6 and 10 times the quantity of the reaction mixture, whereupon the product precipitates in the form of a gummy mass. After allowing the mixture to stand for a while, the liquid is decanted, fresh absolute alcohol is poured to the gummy residue, whereupon the latter becomes converted into a white powdery mass. After drying, a substance very easily soluble in water is obtained; the chemical analysis shows the presence of about 3 atoms of sulphur for each two atoms of nitrogen, i. e. in this product 2 groups of sulphonylate are joined to 1 mol of amino-benzene-sulphamide. The product contains varying amounts of water of crystallisation. About 3 mols of water of crystallisation were found.

The presence of the sulphonylate groups can easily be shown by titration by means of indigo carmine.

The chemical compounds containing two groups of sulphonylate will offer in its aqueous solutions much greater a resistance to the effects of air than the derivatives containing only one sulphonylate group. The reaction of the solutions to litmus is alkaline, but to phenol phthaline practically neutral thus remaining within a reaction range very suitable for solutions intended for injection purpose.

The products of the process are employed for pharmaceutical purposes.

In the present specification the expression "alkali metal" includes also "ammonium."

ZOLTÁN FÖLDI