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MANUFACTURE OF p-ALKOXYSALICYLIC ACIDS

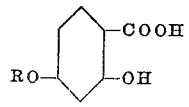
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The present invention relates to the preparation of p-alkoxysalicylic acids of the formula



in which R is a lower alkyl radical.

The alkoxysalicylic acids are important intermediates for the preparation of fluorescent textile brighteners and other products. Formerly, these intermediates were prepared by monoalkylating resolcylic acid. These processes have some disadvantages and require the use of resorcin which is often in short supply as it is a strategic raw material.

According to the present invention, the alkoxysalicylic acids are produced by the diazotization of p-aminosalicylic acid and subsequent alcoholysis. The diazotiazation of p-aminosalicylic acid, and replacement of the diazonium radical, is not a simple operation. If carried out by the conventional procedures, impure products contaminated with colored impurities result, and the yields are entirely unsatisfactory.

The present invention is directed to a simple and efficient method of preparing p-alkoxysalicylic acid from p-aminosalicylic acid. The process involves diazotization by a particular method and alcoholysis with an alcohol corresponding to the alkoxy radical desired. The diazotization procedure requires that the p-aminosalicylic acid and alkali metal nitrite be added to a mineral acid solution. The p-aminosalicylic acid and alkali metal nitrite may be added separately as solids. Preferably, a salt of p-aminosalicylic acid, such as an alkali or alkaline earth metal salt, is first dissolved in water, alkali metal nitrite is added, and the mixed aqueous dispersion is added to a mineral acid to effect diazotization. The mineral acid, of course, transforms the nitrite and p-aminosalicylate into the free acids at the moment of diazotization. In this manner side reactions and the production of colored impurities are reduced to negligible amounts or eliminated entirely.

The process of the present invention may be carried out in one of two modifications as a 2-step or single step process using the term "step" to designate an actual sequence of operations rather than a sequence of chemical reactions. In the 2-step process, diazotization of the p-aminosalicylic acid is effected as described above at low temperature producing the diazonium salt which can be isolated as a solid and added to

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hot alcohol to effect alcoholysis. The second modification involves a single reaction mixture and it, in turn, has 2 variants. In the first, the nitrite and p-aminosalicylic acid or its salt are added to a cold mineral acid alcohol solution containing not more than 35% of water based on the alcohol. The alkoxyl group is then introduced by heating the solution. The second variant is to add p-aminosalicylic acid to the alcoholic solution of the mineral acid and diazotize by adding the nitrite at an elevated temperature so that the diazo compound is alcoholized as fast as it is formed. Not only does this latter process save steps, but the control of the diazotization is improved because the presence of the alcohol appears to inhibit, to some extent, side reactions. The exact mechanism whereby the alcohol prevents undesired side reactions is not completely determined and the invention is not limited to any theory of how this takes place.

The alcohols used may be any of the lower alkanols such as methanol, ethanol, propanols, butanols, the various amyl alcohols, and the like. It is an advantage of the invention that a wide variety of lower alkoxy radicals may be introduced into the salicylic acid molecule by a simple and smooth reaction. The amount of water in the reaction mixture at the time of alcoholysis must be limited. In any event, it must not exceed 35%. However, for best results, considerably smaller concentrations of water are preferable. So long as the upper limit is not exceeded the exact amount of water is not critical and this is an advantage of the process and it makes extremely delicate control of the invention unnecessary.

Any of the ordinary mineral acids may be used, such as hydrochloric acid, sulfuric acid, phosphoric acid, etc. When the diazotization is effected in alcohol solution it is advantageous to use dry hydrogen chloride in order to avoid introducing excessive amounts of water into the reaction mixture.

It is not known why the adverse effect of the halide ion is not quite so marked in the present invention as when replacement of the diazonium group by hydroxyl is effected. This constitutes an advantage as it gives more freedom of choice of reactants.

Regardless of the particular modification used, the reaction proceeds smoothly and the final product, p-alkoxysalicylic acid, is readily isolated by conventional means. Thus, the alcohol can be distilled off and the residue extracted with alkali followed by acidification to precipitate the

product, which is of high purity and is obtainable in good yield.

The amount of alcohol required in the present invention is in nowise critical. Obviously, of course, enough alcohol must be present to furnish the alkoxy radical and this constitutes a lower limit. However, it is desirable to operate with an excess of alcohol. This insures completion of the reaction and permits more rapid alcoholysis and increased output from a given equipment. The amount of excess of alcohol is not critical but, of course, enormous excesses do not produce any improved results and, therefore, are economically undesirable.

The invention will be described in greater detail in conjunction with the following specific examples, all parts being by weight unless otherwise specified.

Example 1

A mixture of 30.6 parts of p-aminosalicylic acid and 50 parts of concentrated hydrochloric acid in 400 parts of methanol is diluted with 258 parts of water. The resulting solution is heated to 60–65° and 14.0 parts of sodium nitrite dissolved in 20 parts of water is added gradually. After the addition the methanol is distilled off. The residue is cooled and filtered to give the desired p-methoxy salicylic acid.

Example 2

A mixture of 30.6 parts of p-aminosalicylic acid and 25 parts of concentrated hydrochloric acid in 400 parts of methanol is heated to reflux. There is then gradually added a solution of 14.0 parts of sodium nitrite in 20 parts of water. The addition is so governed that the diazo compound reacts as fast as it is formed, as shown by a negative color reaction with a coupling component, such as R salt, throughout the course of the addition.

The methanol is distilled out of the reaction mixture, which is then digested with aqueous bicarbonate. The resulting solution is filtered and acidified, giving a good yield of p-methoxysalicylic acid.

Example 3

A stream of dry hydrogen chloride is passed into a slurry of 30.6 parts of p-aminosalicylic acid in 394 parts of ethanol until the amine-hydrochloride formation is complete. A solution of 14.0 parts of sodium nitrite in 20 parts of water is added gradually to the hydrochloride slurry while the temperature is maintained at 65°–70°. The reaction mixture is then diluted with 200 parts of water, heated to the boil, and distilled to remove the ethanol. The residue is cooled and filtered, giving a very high yield of p-ethoxysalicylic acid.

Example 4

To a solution of 30.6 parts of p-aminosalicylic acid and 54 parts of 5 N sodium hydroxide in 50 parts of water, there is added a solution of 14.0 parts of sodium nitrite in 20 parts of water. This solution is added gradually to a vigorously refluxing solution of 50 parts of concentrated hydrochloric acid in 160 parts of methanol. The rate of addition is so governed that no excess diazo compound accumulates in the methanol solution. When the addition is complete, the mixture is evaporated to remove the remaining methanol. The solids thus obtained are digested in aqueous sodium bicarbonate, the resulting solution being filtered and acidified with hydrochloric acid. A good yield of p-methoxysalicylic acid is obtained.

Example 5

A solution of 30.6 parts of p-aminosalicylic acid in 400 parts of methanol is cooled to 0° C. There is then added, with cooling to keep the temperature between 0° and 10° C., 29.4 parts of 100% sulfuric acid. To the resulting slurry is gradually added, at a temperature below −5° C. a solution of 14.0 parts of sodium nitrite in 20 parts of water. The mixture is then brought to room temperature, diluted with 200 parts of water, heated to the boil, freed of methanol by distillation, made alkaline with sodium bicarbonate and filtered. Acidification with hydrochloric acid precipitates p-methoxysalicylic acid, which is filtered and dried.

Example 6

A solution is prepared from 30.6 parts of p-aminosalicylic acid, 70 parts of water, 54 parts of 5 N sodium hydroxide solution, and 14.0 parts of sodium nitrite. This is added gradually to 175 parts of 35% hydrochloric acid at 0° C. The resulting slurry of diazo compound is salted with 10 parts of sodium chloride to further completeness of precipitation, and then filtered at 0° C. The product is added to 200 parts of boiling methanol, and refluxed until the diazo compound is completely consumed as shown by the failure to give any reaction with a coupling component.

The reaction mixture is evaporated and extracted with sodium bicarbonate solution. Acidification gives the desired p-methoxysalicylic acid, which is filtered and dried.

Example 7

A solution of 29.4 parts of 100% sulfuric acid in 160 parts of methanol is cooled to −5° C. To this solution is added gradually and simultaneously a solution of 30.6 parts of p-aminosalicylic acid in 240 parts of hot methanol, and a solution of 14.0 parts of sodium nitrite in 20 parts of water. During this opertaion the temperature is maintained below 5° C. The reaction mixture is then brought to room temperature, diluted with 200 parts of water, heated to the boil, and distilled to remove the methanol. The residue is cooled, filtered, dissolved in aqueous sodium bicarbonate, filtered with decolorizing charcoal, and acidified to precipitate the p-methoxysalicylic acid.

Example 8

The procedure of the preceding example is followed, except that the sulfuric acid is replaced by 50 parts of concentrated hydrochloric acid. Essentially similar results are obtained.

Example 9

To a solution of 30.6 parts of p-aminosalicylic acid in 400 parts of methanal there is added 50 parts of concentrated hydrochloric acid. The resulting mixture is cooled to 0° C. and gradually treated with 14.0 parts of ground sodium nitrite. No excess of nitrite is present until the end of the reaction. The mixture is thoroughly stirred at 0° C. and then gradually brought to room temperature.

The reaction mixture is brought to the boil and freed of the greater part of the methanol by distillation. The residue is cooled and filtered, giving a very high yield of p-methoxysalicylic acid.

Example 10

To a mixture of 30.6 parts of p-aminosalicylic acid and 24 parts of 5N sodium hydroxide solution is added 208 parts of N sodium nitrite solution. This is followed by an additional 24 parts of 5N sodium hydroxide, together with a few crystals of sodium hydrosulfite to discharge any red color which develops. This solution is gradually added at 0–5° to a solution of 62 parts of 96–7% sulfuric acid in 31 parts of water and the brown solution so obtained is added to 790 parts of boiling methanol. The resulting vigorous reaction rapidly consumes the diazo compound. The bulk of the remaining methanol is distilled off. The residue is cooled, filtered, dissolved in sodium bicarbonate solution, filtered with decolorizing charcoal, and acidified to precipitate the p-methoxysalicylic acid.

We claim:

1. A process of producing a p-lower alkoxysalicylic acid which comprises introducing simultaneously p-aminosalicylic acid and a nitrite into a lower alkanol solution of mineral acid maintained at a temperature greater than 60° C., the reaction mixture containing not more than 35% by weight of water based on the lower alkanol.

2. A process of producing a p-methoxysalicylic acid which comprises introducing simultaneously p-aminosalicylic acid and a nitrite into a methanol solution of mineral acid maintained at a temperature greater than 60° C., the reaction mixture containing not more than 35% by weight of water based on the methanol.

3. A process of producing a p-ethoxysalicylic acid which comprises introducing simultaneously p-aminosalicylic acid and a nitrite into an ethanol solution of mineral acid maintained at a temperature greater than 60° C., the reaction mixture containing not more than 35% by weight of water based on the ethanol.

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