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PREPARATION OF S-ARYL-THIOSULFURIC ACIDS

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11 Claims. (Cl. 260—453)

This invention relates to an improved process of preparing salts of certain S-aryl-thiosulfuric acids often referred to as Bunte salts. More specifically it relates to an improved process of preparing water-soluble salts of S-3-nitrophenyl-thiosulfuric acid and S-2-benzoylamino-phenyl-thiosulfuric acid. Salts of the first of the two acids referred to are of particular interest as they are effective veterinary agents for the prevention and treatment of coccidiosis in chickens. The salts can also be hydrolyzed in the present of mineral acids to 3-nitrobenzene thio and because of the cheapness of the process of the present invention this represents an improved method of producing pure 3-nitrobenzene thiol.

A process for the preparation of salts of S-3-nitrophenyl thiosulfuric acid was developed and is described and claimed in our copending application Serial No. 355,178, filed May 14, 1953. This process involved the transformation of bis-(3-nitrophenyl)-disulfide into the sulfenyl chloride, reaction with an amine to form the sulfenyl amide and finally reaction with sulfurous acid in alcohol and water. Although this process represented a feasible commercial process, the number of steps involved kept the cost higher than is desirable.

According to the present invention we have found that the corresponding disulfides can be transformed into salts of the S-thiosulfuric acids in a single step process by reaction with a bisulfite in a solvent mixture containing water and also having a solvent action on the disulfide. For practical operation we have found that methanol, ethanol, or other lower paraffin alcohols containing water as a minor component constitute the preferred solvent mixture although the invention is not limited thereto and other aqueous mixtures having adequate solubility for the disulfides may be used.

The overall reaction of the process of the present invention may be represented as follows:

$$2ArS—SAr+6MeHSO_3 \rightarrow 4ArS—SO_3Me+Me_2S_2O_3+3H_2O$$

in which equation Ar stands for the aryl residue and Me for a base cation. While the reaction takes place in a single step as far as equipment and reaction medium is concerned, we believe that probably the reaction proceeds in two stages. This mechanism is represented by the following equations:

$$4ArS—SAr+4MeHSO_3 \rightarrow 4ArSH+4MeO_3S—SAr$$

$$4ArSH+2MeHSO_3 \rightarrow 2ArS—SAr+Me_2S_2O_3+3H_2O$$

It will be seen that the thiol which is produced in the first reaction is reoxidized to the disulfide by more bisulfide, regenerating half of the amount of disulfide which is reflected in the disulfide figures in the equation that represents the overall reaction. While, as might be expected, it is not possible to obtain completely rigorous proof of the reaction mechanism as the two reactions are proceeding at the same time, the evidence for this reaction mechanism is extremely strong and, therefore, although it is not desired to limit the invention to any particular theory, the evidence is so strong that the mechanism has a high degree of probability. We have determined that the second reaction, namely oxidation of the thiol by bisulfide, actually does take place. The oxidation of thiols is not limited to 3-nitrobenzene thiol and 2-benzoylamino-benzene thiol but it may take place with any thiol having a sufficiently high oxidation-reduction potential, for example 2-naphthalenethiol and benzenethiol.

The use of bisulfites in the reaction of the present invention is a very critical factor. Sulfurous acid will not produce the results of the present invention although it has been used with aryl-disulfides having basic substituents which are, of course, entirely different from those with which the present invention deals. Sulfites are also not useful. It is not known why neither sulfurous acid, which does react with basically substituted aryl-disulfides, nor why sulfites do react in the present process. It is therefore not intended to limit the invention to any theory of why only bisulfites may be used. While the use of the bisulfite is an extremely critical factor in the present invention the particular bisulfite to be used is not critical, in other words, the cation in the salt makes very little difference. Thus alkali metal bisulfites such as sodium and potassium may be used and also ammonium bisulfites and bisulfites of amines such as diethylamine, aniline, cyclohexylamine, piperidine, benzylamine, and the like. The preferred bisulfites are those of sodium and potassium as they are very effective and are cheaper than the other bisulfites which, while operative, present no advantage to offset their higher cost. When the preferred solvent, aqueous methanol, is used there is a definite advantage in using potassium bisulfite in the reaction with bis-(3-nitrophenyl)-disulfide as the potassium salt of the resulting 3-nitrophenyl thiosulfuric acid has a low solubility in methanol and therefore can be readily crystallized in a pure state when the hot clarified reaction mixture is cooled. The higher solubility of the sodium salt makes its recovery more complicated and more than offsets the somewhat lower price of sodium bisulfite.

It has been pointed out above that sulfurous acid, which results when sulfur dioxide is used in an aqueous medium, will not perform the function of the bisulfite in the process of the present invention. However, the presence of free sulfurous acid has no adverse effect provided there is present a sufficient amount of the bisulfite to carry out the reaction. As a result it is sometimes advantageous for practical operation to maintain a small excess of free sulfurous acid in the reaction mixture because this insures against the formation of any neutral sulfite and so makes a very careful supervision of the reaction unnecessary.

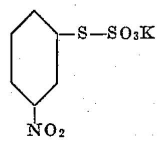
In contradistinction to the criticality of the bisulfite it is an advantage that the temperature is not critical. In general it should be somewhat elevated as the reaction is very slow at room temperature. However, at any temperatures above 40° C. the reaction proceeds readily and no careful control of the temperature is necessary. In practical operation on a large scale, however, it is advantageous to permit the aqueous methanol reaction mixture to boil under a reflux as this provides automatically a temperature which is within the range of good results.

It is a further advantage of the process of the present invention that it does not have to be operated in the absence of oxygen or light as neither appears to affect the reaction adversely and so a simple operating procedure may be used without special precautions.

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

EXAMPLE 1

Potassium salt of S-3-nitrophenyl-thiosulfuric acid

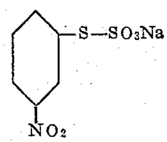


Sulfur dioxide is passed into a solution of 3.8 parts of potassium hydroxide in 60 parts of methanol until a slight excess of sulfur dioxide is present. 4.6 parts of bis-(3-nitrophenyl)-disulfide and 5 parts of water are added. This mixture is refluxed with agitation until the reaction is complete. During this time the initial slurry turns slightly yellow and a large portion of the solid goes into solution. One part of potassium hydroxide is added to neutralize the excess bisulfite. The slurry is filtered hot and the undissolved material is washed with 20 parts of hot methanol. On cooling, the potassium salt separates in nice crystals and high yield. It is recovered by filtration. The potassium salt melts at 195–198° C. with decomposition.

The above procedure is repeated replacing the methanol with an equivalent amount of ethanol. The results obtained are substantially the same.

EXAMPLE 2

Sodium salt of S-3-nitrophenyl-thiosulfuric acid

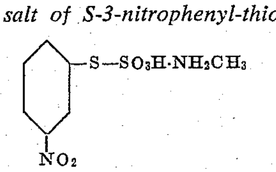


5.7 parts of sodium meta-bisulfite and 4.6 parts of bis-(3-nitrophenyl)-disulfide are slurried in 60 parts of methanol and 5 parts of water. The mixture is refluxed for 2 hours with agitation. 0.6 part sodium hydroxide is added to neutralize the excess bisulfite. The slurry is cooled with stirring to room temperature, filtered, and the solid residue is washed with 40 parts of methanol. The filtrate is evaporated, leaving behind the desired sodium salt somewhat contaminated with sulfite. If desired, it can be free from this contamination by redissolving in 80 parts anhydrous methanol, clarifying, and evaporating. The pure product is obtained in practically quantitative yield.

When ethanol is substituted for methanol the results are similar.

EXAMPLE 3

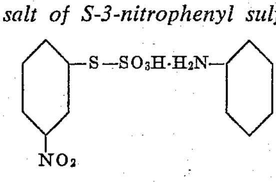
Methylamine salt of S-3-nitrophenyl-thiosulfuric acid



9.24 parts of bis-(3-nitrophenyl)-disulfide and 18.6 parts of a 30% aqueous methylamine solution are added to 80 parts of methanol. Sulfur dioxide is passed into the agitated slurry, causing an exothermic reaction which is finished by refluxing. The resulting solution is concentrated to a small volume whereupon the methylamine salt crystallizes out in good yield and is recovered by filtration.

EXAMPLE 4

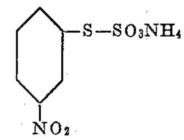
Aniline salt of S-3-nitrophenyl sulfuric acid



The procedure of Example 3 is repeated substituting aniline for the methylamine. The corresponding aniline salt is obtained but the yield is lower than in Example 3.

EXAMPLE 5

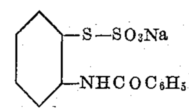
Ammonium salt of S-3-nitrophenyl-thiosulfuric acid



11 parts of 28.6% aqueous ammonia and 9.24 parts of bis-(3-nitrophenyl)-disulfide are added to 80 parts of methanol. Sulfur dioxide is passed into the slurry with agitation. An exothermic reaction occurs. Finally the mixture is refluxed for a short time, cooled, and filtered. By evaporation of the filtrate the ammonium salt is obtained in good yield.

EXAMPLE 6

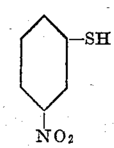
Sodium salt of S-2-benzoylaminophenyl-thiosulfuric acid



6.8 parts of bis-(2-benzoylaminophenyl)-disulfide and 5.7 parts of sodium meta-bisulfite are added to 60 parts of methanol and 5 parts of water. The slurry is refluxed with agitation until the reaction is finished. The hot slurry is filtered and the inorganic residue is washed with about 25 parts of hot methanol. By evaporation of the filtrate the desired sodium salt is obtained in excellent yield.

EXAMPLE 7

3-nitrobenzenethiol



3-nitrobenzenethiol which has never been made by a practical process before can be simply prepared by the following process using the product of Example 1. Two parts of the potassium salt of S-3-nitrophenyl-thiosulfuric acid is added to 30 parts of concentrated hydrochloric acid and the mixture is agitated, air being excluded. After a few hours, an oily layer consisting mainly of the thiol has separated. The mixture is diluted with 30 parts of water and the thiol is extracted with an organic solvent such as benzene. The benzene solution is dried with calcium chloride and leaves on evaporation pure 3-nitrobenzenethiol in quantitative yield. It is an almost colorless liquid which crystallizes only at very low temperature. It forms an orange-red sodium salt when treated with 5N sodium hydroxide solution.

When 3-nitrobenzenethiol is treated with sodium bisulfite in boiling methanol containing a little water, it is oxidized to the bis-(3-nitrophenyl)-disulfide provided that there is not sufficient bisulfite present to cause the reaction described in the previous examples.

We claim:

1. A method of preparing a salt of a S-aryl-thiosulfuric acid selected from the group consisting of S-3-nitrophenyl thiosulfuric acid and S-2-benzoylaminophenyl thiosulfuric acid which comprises reacting compounds selected from the group consisting of bis-(3-nitrophenyl)-disulfide and bis-(2-benzoylaminophenyl)-disulfide with a water soluble bisulfite in an aqueous reaction medium containing a lower paraffin alcohol as the major component.

2. A method according to claim 1 in which the reaction medium is aqueous methanol.

3. A method of producing a salt of S-3-nitrophenyl thiosulfuric acid which comprises reacting bis-(3-nitrophenyl)-disulfide with a soluble bisulfite in an aqueous lower paraffin alcohol reaction medium containing a lower paraffin alcohol as the major component.

4. A method according to claim 3 in which bisulfite is an alkali metal bisulfite.

5. A method according to claim 4 in which the alkali metal bisulfite is potassium bisulfite.

6. A method according to claim 3 in which the reaction medium is aqueous methanol.

7. A method according to claim 6 in which the bisulfite is an alkali metal bisulfite.

8. A method according to claim 7 in which the alkali metal bisulfite is potassium bisulfite.

9. A method according to claim 1 in which the disulfide is bis-(2-benzoylaminophenyl)-disulfide and the salt produced is a S-2-benzoylaminophenyl thiosulfate.

10. A method according to claim 9 in which the reaction medium is aqueous methanol.

11. A method according to claim 9 in which the bisulfite is an alkali metal bisulfite.

No references cited.