

UNITED STATES PATENT OFFICE

2,646,447

PREPARATION OF THIOSEMICARBAZIDE

John Christie Paterson, Westfield, N. J., assignor
to American Cyanamid Company, New York,
N. Y., a corporation of Maine

No Drawing. Application March 8, 1951,
Serial No. 214,631

1 Claim. (Cl. 260—552)

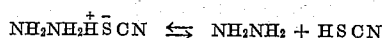
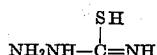
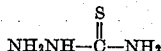
1

This invention relates to a new and improved process for obtaining thiosemicarbazide. Thiosemicarbazide, which has the formula



is a valuable intermediate in the preparation of pharmaceuticals and other organic products.

Thiosemicarbazide was prepared by Freund and Schander in 1896 and reported in vol. 29 of the *Berichte* on page 2501. It is usually obtained by the reaction of hydrazine sulfate with potassium thiocyanate in aqueous solution and rearranging the thiocyanic acid salt of hydrazine so formed by heating the reaction mixture in aqueous solution at the boiling point. Although we are not certain of the intermediate formed during this rearrangement, it would seem that this reaction might follow the steps indicated below:



At the temperature of reaction, the hydrazine salt may decompose into free hydrazine and thiocyanic acid which may recombine as indicated above. The thiosemicarbazide so formed is much less soluble in water than the hydrazine salt and may therefore be separated by crystallization. Only a small percentage of the hydrazine salt can be rearranged in aqueous solution at the boiling point and it was considered necessary to filter off the product which separated out of the reaction mixture 6 or 7 times, and add additional water, in order to obtain satisfactory yields of thiosemicarbazide.

An even greater disadvantage of the earlier method of preparing this product was due to the fact that the rearrangement involved was strongly exothermic, difficult to control, frequently formed worthless by-products and potentially explosive if large amounts of material were heated at one time.

One of the objects of this invention is to provide a process which can be used to prepare com-

2

mercial amounts of thiosemicarbazide without the explosive hazard.

It is an advantage of my invention that the rearrangement to thiosemicarbazide can be readily controlled with the production of fewer undesirable by-products and uniformly good yields of the desired product which can be easily isolated.

I have found that the temperature range for efficient rearrangement is critical and that the above objective may be realized by carrying out the rearrangement step within a particular temperature range under reduced pressure and in the substantial absence of solvents; these three conditions being required for the optimum yield. In my process, dihydrazine sulfate is reacted with an alkali-metal thiocyanate in water and the reaction product smoothly rearranged under reduced pressure within a specific temperature range. I have observed that when the rearrangement takes place under these specific conditions, no difficulty is experienced in controlling the reaction, regardless of the the quantity involved.

In practicing this invention, hydrazine sulfate is first converted to the dihydrazine salt in aqueous medium by means of an alkaline agent such as caustic soda or soda ash. An alkali-metal thiocyanate such as sodium or potassium thiocyanate is then added and solution heated for a short time at 80°–90° C. Upon partial cooling, alcohol is added and the slurry cooled to room temperature, at which point the sodium sulfate is removed by filtration. The filtrate, which is a solution of hydrazine thiocyanate, is then distilled at low temperature under reduced pressure until no more water distills over. This distillation under reduced pressure automatically assures that the temperature of the reaction mass will not reach dangerously high temperatures so long as solvent is present. After the water has been removed, the residual mass is heated under reduced pressure within the range of about 90°–105° C., during which latter time the rearrangement occurs without decomposition of the desired product.

It should be noted that no rearrangement takes place during the stage of vacuum distillation of the alcohol and water. This rearrangement occurs only at temperatures above 68° C., and at the operating pressure this temperature will not be obtained until the solvents have been removed.

Whereas I have expressed an operating range of from 90° to 105° C., it will be found that in working with small batches the upper limit may be exceeded somewhat. Subsequent examples will show, however, that 90° C. is a practical lower

3

limit, as the yield is unsatisfactory when the reaction is carried out below this temperature. For optimum yield combined with satisfactory control of the explosion hazard, the temperature range is very critical and I prefer to carry out the reaction at between 95° and 100° C. at a pressure of approximately 10 mm. to 30 mm. of mercury.

Other hydrazine salts and other alkali thiocyanates may be substituted for dihydrazine sulfate and sodium thiocyanate without impairing the yield.

The thiosemicarbazide obtained by the process illustrated in the following examples is of excellent quality as indicated by the melting point of the product obtained. It will be recognized, however, that the melting point may vary a few degrees from batch to batch.

Example 1

A solution of dihydrazine sulfate was prepared by adding 130 g. of hydrazine sulfate to 300 ml. of water and then adding 55.5 g. of soda ash. The pH of the solution was now approximately 5.0-5.4. 99.7 g. of sodium thiocyanide was then added and the solution heated at 95° C. for 30 minutes. On cooling to 65-70° C., 200 ml. ethanol was added and the slurry taken to 5° C., where it was filtered and the filter cake washed with 100 ml. ethanol. The filtrate volume was approximately 325 ml. The pH of the solution was adjusted to 3.0-6.0 with mineral acid, and then the water and alcohol were distilled off under 10 mm. vacuum at low temperature. The heel was then heated under vacuum at 100° C./10 mm. for 3½ hours and then taken up in 500 ml. water. After a Darco treatment with filtration, the filtrate was cooled to 0° C. and the product filtered off and dried. Yield: 60.6 g., M. P. 181-182° C.

By distilling the mother liquor from Fraction 1 under vacuum and rearranging under vacuum for 3 hours at 95-100° C. and then taking up in 350 ml. water and purifying as above, an additional 5.0 g. of product was obtained, M. P. 179-180° C. Total yield 72.2% of theoretical.

The thiosemicarbazide obtained from both fractions was of sufficient purity to warrant its direct use in the preparation of pharmaceuticals.

Example 2

The critical nature of this rearrangement even when dealing with laboratory quantities was forcibly demonstrated by a repetition of Example 1, using three times that quantity of reactants. The hydrazine thiocyanate was heated under 10 mm. vacuum above 105° C. At 108° C. the temperature rise became uncontrollable and in an additional 18 minutes rose 14 degrees to 122° C. Seven minutes later the temperature had risen to 175° C. External cooling failed to check this rapid rise in temperature. During this rapid rise in temperature, there was a simultaneous drop in vacuum until the vacuum was finally released at 130° C. Large amounts of H₂S gas were given off and no attempt was made to salvage any product from this reaction mixture.

Example 3

A solution of dihydrazine sulfate was prepared by adding 390 g. of hydrazine sulfate to 900 ml. water and then adding 158 ml. of 50% caustic, the resulting pH being 4.7. 299 g. of sodium thiocyanate were then added and the solution

4

heated at 95° C. for 30 minutes. Upon cooling to 60°, 400 ml. of ethanol were added and then the reaction mixture was cooled at 15° C. at which temperature the Glauber's salt was filtered off. The pH of the filtrate was adjusted to 3.0-6.0. The alcohol and water were then distilled off at low temperature at 20 mm. vacuum and the heel was heated at 100±2° C. and 10 mm. pressure for 3½ hours. The heel was then taken up in 1500 ml. water and given a Darco treatment and filtration. The filtrate was cooled to 0° C. and the thiosemicarbazide filtered off. Yield: 160 g., M. P. 180° C. A second crop from Fraction 1 mother liquor was obtained by distilling off the water under vacuum and by heating the heel under vacuum at 98° C. for 3 hours. Yield: 31.5 g. or 70.25% of theoretical.

Example 4

Example 3 was repeated except that the rearrangement was carried out at 80-85° C. for 6 hours under vacuum. The yield was 47.5 g. (17.25% of theoretical), M. P. 179° C.

Example 5

Example 3 was repeated except that the rearrangement was carried out at 93° C. for 4 hours.

Yield:

Fraction 1, 138.3 g., M. P. 180°, 50.7%	} 75.5%
Fraction 2, 68.0 g., M. P. 179°, 24.8%	

Example 6

Example 5 was repeated except that the rearrangement was carried out at atmospheric pressure after the water and alcohol had been distilled off. All of the solvent distilled over under 68° C. at 30 mm. The vacuum was then broken and the rearrangement carried on at 95-99° C. for 8 hours at atmospheric pressure. The yield of Fraction 1 was only 44.5% of theoretical. No second fraction was isolated.

Example 7

Example 7 was similar to Example 3 except that for Fraction 1 the rearrangement was run at 85-90° C. Yield: 54.5 g., M. P. 180-181° C., equivalent to 20% of theoretical. The water was removed at low temperature under vacuum from Fraction 1 mother liquor and a second rearrangement was carried out at 96-100° C., the yield of product melting at 180-181° C. being 39% of theoretical.

This demonstrates that the yields obtained at temperatures less than 93° C. are greatly inferior to those obtained when the rearrangement was carried out between 93-105° C. (See Example 3.)

Example 8

Example 3 was repeated except that the sodium thiocyanate was replaced by an equivalent amount of potassium thiocyanate. The total yield (Fractions 1 and 2) of thiosemicarbazide melting at 180° C. was 190 g.

Example 9

Following the directions given in Example 3, a plant batch gave a yield of 149 pounds Fraction 1, equivalent to 51.4%, M. P. 179-180° and Fraction 2, 32 pounds equivalent to 11.7%. This material was used satisfactorily in the production of a pharmaceutical.

When the temperature during rearrangement reached 100° C. cooling water was run through

5

the jacket for one minute and instantly there was a sharp drop in temperature. This demonstrated the ease of control of reaction temperature in large scale operations.

This invention is not limited to the exact details shown and described for obvious modifications will occur to persons skilled in the art.

I claim:

A process for obtaining thiosemicarbazide of the formula



6

which comprises rearranging the thiocyanic acid salt of hydrazine in the substantial absence of any solvent by heating to a temperature between 90° C. and 105° C. at reduced pressure.

JOHN CHRISTIE PATERSON.

References Cited in the file of this patent

UNITED STATES PATENTS

Number	Name	Date
2,450,406	Bambas	Oct. 5, 1948