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## METHOD OF PREPARING 2,6-DIKETOPURINES

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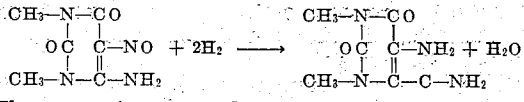
This invention relates to nitroso compounds and more particularly to the reduction of nitroso compounds.

Among the objects of this invention are the provision of methods for the reduction of nitroso compounds; the provision of methods of the type referred to in which the reduction is carried out catalytically; the provision of methods of the type referred to in which the reduction is easily and quickly carried out at relatively low cost; and the provision of methods of the type indicated in which the resulting reduced product is particularly adapted for subsequent processing. Other objects will be in part apparent and in part pointed out hereinafter.

The invention accordingly comprises the steps and sequence of steps, and features of synthesis, analysis, or metathesis, which will be exemplified in the processes hereinafter described, and the scope of the application of which will be indicated in the following claims.

In accordance with the present invention, it has been found that nitroso compounds of the type of 4-amino-5-nitrosouracil can be reduced catalytically with hydrogen gas. The reduction is easily carried out with recovery of substantially all of the catalytic material employed if desired. Among the catalysts which have been found effective for this reaction are nickel, palladium and platinum. It is preferred that the catalyst be in a state of relatively fine subdivision.

The process of the present invention may be illustrated by the catalytic reduction of 1,3-dimethyl-4-amino-5-nitrosouracil:



The present process, however, is also applicable to the reduction of the corresponding nitroso compounds having a single methyl group in either the one or three position or in which both positions contain no substituents.

The reduction of the nitroso compound to the corresponding diamino compound may be carried out at ordinary temperatures and pressures merely by reducing the nitroso compound in a mixture containing the catalyst suspended in an inert medium such as water or alcohol. This suspension should be agitated sufficiently vigorously to give a very fine dispersion of hydrogen in the inert medium. Alternatively, other methods may be adopted which provide a fine dispersion of the gaseous particles of the hydrogen throughout the reaction mixture. Higher temperatures may be used if desired, although, since this is not necessary, it is preferred that the reaction be carried out at approximately room temperature. In general, the reaction temperature should not be permitted to rise substantially above 85° C. However the preferred reaction conditions under which the best yields have been obtained are temperatures not substantially in excess of 55° C.

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The reaction may be conveniently carried out at atmospheric pressures, although if desired elevated pressures may be employed. They are not essential for carrying out the reaction.

The hydrogen may be diluted with inert gases, such as nitrogen, without interfering with the reaction. Accordingly, mixtures of nitrogen and hydrogen obtained as by the cracking of ammonia may be utilized for this purpose.

After completion of the reaction and removal of the catalyst, the solution of dimethyldiaminouracil is well adapted for conversion to the formyl derivative. This can be easily accomplished by the formation of the formyl compound in the usual way.

The formyl compound may then be used in the customary manner for the preparation of theophylline. The reduced compound is not only obtained economically and in high yield, but the product of the present process is substantially free of salts and other impurities which would have been introduced by customary reduction methods.

While water constitutes the preferred suspending medium, other inert substances may likewise be present. The reaction may be carried out under acid or alkaline conditions; e. g., where an acid such as formic acid or acetic acid is used, or an alkaline reagent such as ammonia. If the catalyst employed is acid-soluble, the proportion of the acid and its concentration should not be such as to destroy the activity of the catalyst.

The following examples illustrate the invention:

*Example 1*

A one-liter, three-necked flask was fitted with a mechanical stirrer, hydrogen inlet tube and thermometer. The stirrer was a piece of stainless steel wire one-sixteenth inch in diameter attached in a loop about three inches across to a ¼ inch diameter shaft fitted with a gas-tight stuffing box and driven at high speed by a motor. The hydrogen inlet was attached to a supply of hydrogen at atmospheric pressure in a gasometer. The flask was charged with 1,3-dimethyl-4-amino-5-nitrosouracil monohydrate (55 g., 0.27

mole), distilled water (500 ml.), and reduced nickel catalyst (3 g.). The flask was flushed out with hydrogen. The stirrer was started and hydrogen began to be absorbed. The temperature of the reaction mixture was 28° C. at the beginning and rose gradually to 37° C. A total of 13.2 liters of hydrogen was absorbed during four hours. The red color of the nitroso compound had disappeared and hydrogen absorption stopped. The reaction mixture contained a suspension of small, colorless crystals of 1,3-dimethyl-4,5-diaminouracil. Dimethyldiaminouracil may be brought into solution by gentle warming and the nickel catalyst may be separated by decantation or filtration. The catalyst usually retains its activity and can be reused.

The solution of diamino compound, after separation of the nickel catalyst, was acidified with 30 ml. of 87% formic acid and heated at 90–95° C. for 30 minutes. The solution now contained the formyl derivative of 1,3-dimethyl-4,5-diaminouracil which crystallizes on cooling the solution and may be recovered.

The hot solution of the formyl derivative was neutralized to phenolphthalein indicator by adding 40 ml. of 10N sodium hydroxide solution and then an excess of 45 ml. more of the alkali was added. The strongly alkaline solution was heated at 90° C. for 10 minutes to convert the formyl compound to theophylline. The solution was acidified with sulfuric acid and allowed to cool; theophylline separated in crystalline form. The first crop weighed 36.4 g. A second crop amounting to 5.2 g. was obtained by saturating the solution with sodium sulfate. The crude product was recrystallized from water giving 40.8 g. of pure theophylline amounting to 79% of the theoretical yield based on the 1,3-dimethyl-4-amino-5-nitrosouracil used as starting material.

*Example 2*

A flask of 500 ml. capacity arranged on a shaking machine for catalytic hydrogenation was charged with water (200 ml.), 1,3-dimethyl-4-amino-5-nitrosouracil (10 g.), acetic acid (25 ml.), palladium chloride (3 ml. of 1% solution) and gum arabic (3 ml. of 1% solution). The flask was flushed out with hydrogen from a gasometer at atmospheric pressure and shaken at room temperature. A total of 2550 ml. of hydrogen was absorbed during seven hours. The red color of the nitroso compound had disappeared and the solution contained 1,3-dimethyl-4,5-diaminouracil in high yield as shown by its conversion to theophylline as described in Example 1.

*Example 3*

An apparatus similar to that described in Example 2 was used except that the flask was of 125 ml. capacity. 1,3-dimethyl-4-amino-5-nitrosouracil (2 g.), water (40 ml.), and platinum dioxide catalyst (0.1 g.) were placed in the flask and shaken with hydrogen at room temperature and atmospheric pressure. A total of 495 ml. of hydrogen was absorbed in two hours and the red color of the nitroso compound disappeared. The solution contained 1,3-dimethyl-4,5-diaminouracil in high yield.

*Example 4*

4-amino-5-nitrosouracil (1.75 g.) suspended in water (40 ml.) was reduced in the apparatus described in Example 3. The catalyst was platinum dioxide (0.1 g.). A total of 470 ml. of hydrogen was absorbed in two hours and the red color of the nitroso compound disappeared. The flask contained a suspension of 4,5-diaminouracil.

*Example 5*

1,3-dimethyl-4-amino-5-nitrosouracil (2 g.), alcohol (40 ml.), and nickel catalyst (0.3 g.) were placed in a flask and shaken with hydrogen at room temperature and atmospheric pressure as described in Example 3. A total of 580 ml. of hydrogen was absorbed in two hours and the red color of the nitroso compound disappeared. The solution contained 1,3-dimethyl-4,5-diaminouracil in high yield.

*Example 6*

An apparatus similar to that described in Example 3 was charged with 1,3-dimethyl-4-amino-5-nitrosouracil (6 g.), water (40 ml.), concentrated ammonia (5 ml.), and nickel catalyst (1 g.). The flask was flushed with hydrogen and shaken at room temperature. Hydrogen was absorbed and the red color of the nitroso compound disappeared. The reduction was complete in three hours, the solution containing the 1,3-dimethyl-4,5-diaminouracil product.

*Example 7*

The procedure described in Example 7 was repeated except that the concentrated ammonia was omitted from the reagents and 5 ml. of glacial acetic acid was added. The reduction proceeded with absorption of hydrogen and disappearance of the red color of the nitroso compound. When the reduction was complete the solution contained 1,3-dimethyl-4,5-diaminouracil.

The reduction of a 4-amino-5-nitrosouracil can be carried out at ordinary temperature and pressure by hydrogen and a reducing catalyst such as nickel, palladium or platinum. Nickel is the preferred catalyst. The nitroso compound and catalyst should be suspended in an inert medium such as water or alcohol and the agitation or shaking must be sufficiently vigorous to give a very fine dispersion of the hydrogen in the inert medium. High pressures may be used. The hydrogen may be diluted with inert gases such as nitrogen, from cracked ammonia for example, without interfering with the reaction but provision must be made for suitable elimination of the diluent. The reaction may be conducted over a wide range of temperatures but for best results it is generally preferred to operate below 85° C.

After completion of the reaction and removal of the catalyst the solution of the dimethyl diaminouracil is well adapted for conversion to the formyl derivative which can be easily accomplished by the addition of formic acid and heating. The advantage of using a catalytic reduction is its economy of materials and production of the product, obtained in high yield, in a solution free of salts or other impurities.

The reduction is conveniently carried out using water as a suspending medium but it is possible to have present other inert substances or even acids or bases such as formic or acetic acid or ammonia. If nickel is used as a catalyst the amount and concentration of acid should not be such as to dissolve the metal.

In view of the above, it will be seen that the several objects of the invention are achieved and other advantageous results attained.

As many changes could be made in the above processes without departing from the scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.

I claim:

1. The method of reducing a 4-amino-5-nitrosouracil to a 4,5 diaminouracil which comprises reacting said nitroso compound with hydrogen at a temperature not substantially in excess of 85° C. and in the presence of a catalyst selected from a group consisting of nickel, palladium and platinum.

2. The method of reducing a 4-amino-5-nitrosouracil to a 4,5 diaminouracil which comprises reacting said nitroso compound with hydrogen at a temperature not substantially in excess of 85° C. and in the presence of a nickel catalyst.

3. The method of reducing a 4-amino-5-nitrosouracil to a 4,5 diaminouracil which comprises reacting said nitroso compound with hydrogen at a temperature not substantially in excess of 85° C. and in the presence of a palladium catalyst.

4. The method of reducing a 4-amino-5-nitrosouracil to a 4,5 diaminouracil which comprises reacting said nitroso compound with hydrogen at a temperature not substantially in excess of 85° C. and in the presence of a platinum catalyst.

5. The method of reducing the nitroso group of 1,3-dimethyl-4-amino-5-nitrosouracil to convert the nitroso group to an amino group which comprises reacting said compound with hydrogen at a temperature not substantially in excess of 85° C. and in the presence of a catalyst containing at least one metal selected from the group consisting of nickel, palladium and platinum.



6. The method which comprises reacting a 4-amino-5-nitrosouracil with hydrogen at a temperature not substantially in excess of 85° C. and in the presence of a catalyst selected from the group consisting of nickel, palladium and platinum to form a 4,5-diaminouracil, formylating the product by reaction with formic acid, and cyclizing the formylated compound with an alkali to form a purine, said formylation and cyclizing being carried out without isolation of intermediates.

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