

# PATENT SPECIFICATION

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790,066

Date of filing Complete Specification June 4, 1956.

Application Date June 16, 1955.

No. 17334/55.

Complete Specification Published Feb. 5, 1958.

Index at acceptance:—Class 2(3), C2B(21: 37F1: 37F4).

International Classification:—C07c.

## COMPLETE SPECIFICATION

### Preparation of Semicarbazones

We, WHIFFEN & SONS LIMITED, a British company of Aldersgate Chemical Works, Carnwath Road, Fulham, London, S.W.6, do hereby declare the invention for which we pray

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that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

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The present invention relates to the production of semicarbazones.

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A standard organic chemical reaction is the formation of semicarbazones by the condensation of aldehydes and ketones with semicarbazide. This reaction finds utility in the laboratory in the examination of compounds and commercially in the separation of various aldehydes and ketones. The instability of semicarbazide base necessitates the storage of this material in the form of some simple derivative such as a salt commonly the hydrochloride or as acetone semicarbazone. In order to make the semicarbazide available for the production of semicarbazones, the derivatives such as acetone semicarbazone require hydrolysis and salts such as semicarbazide hydrochloride require treatment with for example sodium acetate.

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It has now been found that semicarbazide may be prepared more economically by the reaction of hydrazine and nitrourea and that the reaction product may be suitably used for the production of semicarbazones. An additional advantage of such process is that the reaction is carried out in the absence of inorganic contaminants.

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Accordingly the present invention is for a process for the production of semicarbazones wherein an aldehyde or ketone is treated with the reaction of hydrazine and nitrourea.

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The manner and order of admixture of the reactants may be varied, thus the hydrazine and nitrourea may be reacted together and the carbonyl compound added to the resulting reaction product, or alternatively the carbonyl

compound may be admixed with nitrourea and hydrazine added subsequently or the carbonyl compound may be admixed with hydrazine and the nitrourea added subsequently.

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A further alternative is to add the hydrazine and nitrourea together or separately to the carbonyl compound in the presence of water.

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It has been found that a salt of hydrazine and nitrourea may be prepared, and the present invention embodies as a new compound the hydrazine salt of nitrourea, as well as the use of this new compound in the production of semicarbazones.

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The hydrazines salt of nitrourea may be prepared for example by the reaction of aqueous hydrazine hydrate and nitrourea, from which the colourless crystalline salt may be precipitated by the addition of a solvent such as alcohol.

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The readiness with which semicarbazones are formed varies with the nature of the carbonyl compound and it has been found that in the case of carbonyl compounds which form semi-carbazones readily any of the above methods may be used satisfactorily, whereas in the case of carbonyl compounds which only form semicarbazones with difficulty one of the above methods may be found more satisfactory than the others. In general in cases of difficulty the first method wherein the hydrazine and nitrourea are reacted together and the carbonyl compound added subsequently may be found the most satisfactory.

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The reaction between the hydrazine and nitrourea takes place in aqueous solution and may be assisted by the use of elevated temperatures. The hydrazine may be employed in the form of any functional derivative such as hydrazine hydrate or hydrazine salts such as hydrazine sulphate, hydrazine hydrochloride and hydrazine acetate. The formation of the semicarbazones may take place under pH conditions over a wide range for example in the range about pH 2 to pH 11, it being desirable

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to avoid conditions of either excessive acidity or excessive alkalinity. It is now considered that the optimum pH conditions for the formation of semicarbazones are of the order of pH 3.5—4.0. The formation of the semicarbazone may be assisted by the presence in the reaction medium of some acetic acid.

If so desired a solid mixture of nitrourea and a solid hydrazine functional derivative for example hydrazine sulphate may be prepared, suitably with these compounds in substantially equimolecular proportions, and used directly as the reagent for the production of semicarbazones.

The process of the present invention may be applied with advantage to the preparation of semicarbazones of carbonyl compounds such as 5-nitro-furfuraldehyde and sex hormones. If so desired the carbonyl compound may be formed *in situ* in the reaction. Thus for example in the case of 5-nitrofurfuraldehyde this may be prepared by the hydrolysis of 5-nitrofurfurylidene diacetate and the product obtained used for the formation of 5-nitrofurfural semicarbazones.

The following examples are given to illustrate the process of the present invention. The parts by weight and parts by volume bear the same relation to each other as do grams to millilitres. The percentages quoted are by weight:—

#### EXAMPLE 1.

18.2 parts by weight of nitrourea, 14.5 parts by volume of 60% aqueous hydrazine hydrate and 50 parts by volume of water were mixed together and warmed to a temperature of 60—65° C. Nitrous oxide gas was evolved and when this had ceased the mixture was cooled to about 20° C., 5 parts by volume of glacial acetic acid added thereto and then 15 parts by volume of benzaldehyde were added slowly to the mixture with stirring. The precipitated benzaldehydesemicarbazone was recovered in 89% yields.

#### EXAMPLE 2.

24.3 parts by weight of 5-nitrofurfurylidene diacetate and 15 parts by volume of concentrated sulphuric acid (specific gravity 1.84) were mixed together and warmed until solution was obtained.

The solution was cooled, diluted with 250 parts by volume of water and cooled again and to the solution 10.5 parts of nitrourea were added with stirring and then 5 parts by volume of 100% hydrazine hydrate. The precipitated 5-nitrofurfuralsemicarbazone was separated and recovered in 93% yield.

#### EXAMPLE 3.

100 parts by weight of nitrourea were dissolved with cooling in 80 parts by weight of 60% hydrazine hydrate and alcohol added to the clear solution to precipitate 128 parts by weight of the colourless crystalline salt melting at 89° C. with gas evolution.

100 parts by weight of the hydrazine salt of nitrourea prepared in this way were dissolved in 500 parts of water and the solution maintained at 60° C. until the evolution of nitrous oxide ceased. A few parts of glacial acetic acid were then added and 77 parts by weight of benzaldehyde introduced dropwise with mechanical stirring giving 95 parts by weight of benzaldehyde semicarbazone of melting point 219° C.

What we claim is:—

1. A process for the preparation of semicarbazones which comprises treating an aldehyde or ketone with the reaction product of hydrazine or its functional derivatives or salts and nitrourea.

2. A process according to Claim 1 which comprises reacting together hydrazine or its functional derivatives or its salts and nitrourea and subsequently adding an aldehyde or ketone to the resulting reaction product.

3. A process according to Claim 1 which comprises admixing nitrourea and an aldehyde or ketone and subsequently reacting the mixture with hydrazine or its functional derivatives or its salts.

4. A process according to Claim 1 which comprises admixing hydrazine or its functional derivatives or its salts and an aldehyde or ketone and subsequently reacting the mixture with nitrourea.

5. A process according to any one of the preceding claims wherein the reaction is carried out in the presence of water.

6. A process according to any one of the preceding claims wherein the reaction is carried out at an elevated temperature.

7. A process according to any one of the preceding claims wherein the reaction is carried out at a pH ranging from pH 2 to pH 11 preferably pH 3.5 to pH 4.

8. A process according to any one of the preceding claims wherein said hydrazine derivative is hydrazine hydrate.

9. A process according to any one of the preceding claims wherein said hydrazine salt is hydrazine sulphate, hydrazine hydrochloride or hydrazine acetate.

10. A process according to any one of the preceding claims wherein said aldehyde or ketone is 5-nitrofurfuraldehyde or a sex hormone.

11. A process for the preparation of semicarbazones substantially as described with reference to any of the preceding examples.

12. A process for the preparation of semicarbazones substantially as hereinbefore described.

13. Semicarbazones when prepared by the method according to any one of Claims 1 to 12.

14. The salt of hydrazine and nitrourea.

15. A process for the preparation of the hydrazine salt of nitrourea which comprises reacting together aqueous hydrazine hydrate

and nitrourea and precipitating the salt thus formed by the addition of a solvent such as alcohol.

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## PROVISIONAL SPECIFICATION

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5 We, WHIFFEN & SONS LIMITED, a British company of Aldersgate Chemical Works, Carnwath Road, Fulham, London, S.W.6, do hereby declare this invention to be described in the following statement:—

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A standard organic chemical reaction is the formation of semicarbazones by the coupling of aldehydes and ketones with semicarbazide. This reaction finds utility in the laboratory in the examination of compounds and commercially in the separation of various aldehydes and ketones. The instability of semicarbazide base necessitates the storage of this material in the form of some simple derivative such as a salt commonly the hydrochloride or as acetone semicarbazone. In order to make the semicarbazide available for the production of semicarbazones, the derivatives such as acetone semicarbazone require hydrolysis and salts such as semicarbazide hydrochloride require treatment with for example sodium acetate.

15 It has now been found that semicarbazide may be prepared more economically by the reaction of hydrazine and nitrourea and that the reaction product may be suitably used for the production of semicarbazones. An additional advantage of such process is that the reaction is carried out in the absence of inorganic contaminants.

20 Accordingly the present invention is for a process for the production of semicarbazones wherein an aldehyde or ketone is treated with the reaction product of hydrazine and nitrourea.

25 The manner and order of admixture of the reactants may be varied, thus the hydrazine and nitrourea may be reacted together and the carbonyl compound added to the resulting reaction product, or alternatively the carbonyl compound may be admixed with nitrourea and hydrazine added subsequently or the carbonyl compound may be admixed with hydrazine and the nitrourea added subsequently.

30 A further alternative is to add the hydrazine and nitrourea together or separately to the carbonyl compound in the presence of water.

35 It has been found that a salt of hydrazine and nitrourea may be prepared, and the present invention embodies as a new compound the hydrazine salt of nitrourea, as well as the use of this new compound in the production of semicarbazones.

40 The hydrazine salt or nitrourea may be prepared for example by the reaction of aqueous

hydrazine hydrate and nitrourea, from which the colourless crystalline salt may be precipitated by the addition of a solvent such as alcohol.

45 The readiness with which semicarbazones are formed varies with the nature of the carbonyl compound and it has been found that in the case of carbonyl compounds which form semicarbazones readily any of the above methods may be used satisfactorily, whereas in the case of carbonyl compounds which only form semicarbazones with difficulty one of the above methods may be found more satisfactory than the others. In general in cases of difficulty the first method wherein the hydrazine and nitrourea are reacted together and the carbonyl compound added subsequently may be found the most satisfactory.

50 The reaction between the hydrazine and nitrourea takes place in aqueous solution and may be assisted by the use of elevated temperatures. The hydrazine may be employed in the form of any derivative such as hydrazine sulphate, hydrazine hydrochloride, hydrazine acetate and the like. The formation of the semicarbazones may take place under pH conditions over a wide range for example in the range about pH 2 to pH 11, it being desirable to avoid conditions of either excess acidity or excess alkalinity. It is now considered that the optimum pH conditions for the formation of semicarbazones are of the order of pH 3.5—4.0. The formation of the semicarbazone may be assisted by the presence in the reaction medium of some acetic acid.

55 If so desired a solid mixture of nitrourea and a solid hydrazine derivative for example hydrazine sulphate may be prepared, suitably with these compounds in substantially equimolecular proportions, and used directly as the reagent for the production of semicarbazones.

60 The process of the present invention may be applied with advantage to the preparation of semicarbazones of carbonyl compounds such as 5-nitrofurfuraldehyde, sex hormones, etc. If so desired the carbonyl compound may be formed *in situ* in the reaction. Thus for example in the case of 5-nitrofurfuraldehyde this may be prepared by the hydrolysis of 5-nitrofurfurylidene diacetate and the product obtained used for the formation of 5-nitrofurfuralsemicarbazide.

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by volume of 60% aqueous hydrazine hydrate  
and 50 parts by volume of water were mixed  
together and warmed to a temperature of 60—  
10 65° C. Nitrous oxide gas was evolved and  
when this had ceased the mixture was cooled to  
about 20° C., 5 parts by volume of glacial  
acetic acid added thereto and then 15 parts by  
volume of benzaldehyde were added slowly to  
15 the mixture with stirring. The precipitated  
benzaldehyde semicarbazide was recovered in  
89% yields.

EXAMPLE 2.

- 20 24.3 parts by weight of 5-nitrofurfurylidene  
diacetate and 15 parts by volume of concen-  
trated sulphuric acid (specific gravity 1.84)  
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100 parts by weight of the hydrazine salt of  
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in 500 parts of water and the solution main- 40  
tained at 60° C. until the evolution of nitrous  
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benzaldehyde introduced dropwise with mech-  
anical stirring giving 95 parts by weight of  
benzaldehyde semicarbazone of melting 45  
point 219° C.

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Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press,—1958.  
Published at the Patent Office, 25, Southampton Buildings, London, W.C.2, from which  
copies may be obtained.