951,029

PATENT SPECIFICATION

NO DRAWINGS

951,029

Date of Application and filing Complete Specification: July 31, 1962.

No. 29360/62.

Application made in Germany (No. B63889 IVd/12p) on Sept. 2, 1961.

Complete Specification Published: March 4, 1964.

© Crown Copyright 1964.

Index at acceptance:—C2 C(1J1B, 1J1C3, 1J1E, 1J1Z, 1Q5, 1Q6C, 1Q8A, 1Q9H, 1Q11D, 1Q11G, 1Q11J, 2A1, 2A5, 2B3A1, 2B3E, 2B3G1, 2R18)

International Classification:—C 07 d

COMPLETE SPECIFICATION

New Benzene-Sulphonyl-Semicarbazides

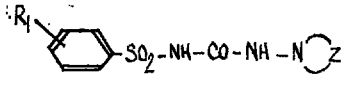
We, C.F. BOEHRINGER & SOEHNE G.M.B.H., a body corporate organised under the laws of Germany, of Mannheim-Waldhof, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with new benzene-sulphonyl-semicarbazides and with the production thereof.

It is known that various benzene-sulphonyl-ureas possess blood sugar lowering properties and are suitable for administration as oral anti-diabetic substances (c.f., for example, Arzneimittel-Forschung, *8*, 448—454/1958). In particular, N_1-sulphanilyl-N_2-(*n*-butyl)-urea and N_1 - (4 - methyl - benzene - sulphonyl) - N_2-(*n* - butyl) - urea have achieved great significance in diabetes therapy.

We have now found that nuclear-halogenated benzene-sulphonyl-semicarbazides, in which the terminal nitrogen atom of the hydrazino group is connected to an alkylene chain containing 3 to 5 carbon atoms to form a ring, possess a very strong blood sugar lowering effect and always have an extraordinarily good compatibility. This good compatibility renders possible, in the case of the use of the new compounds as oral anti-diabetic substances, a substantial differentiation in the treatment of diabetes with regard to the strength effect and duration factors which, also in the case of the individual representatives of this class of compounds, vary in one direction or the other.

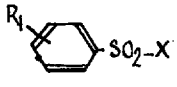
The new benzene-sulphonyl-semicarbazides according to the present invention may be represented by the general formula:—



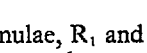
wherein R_1 is a halogen atom and Z is an alkylene radical containing 3 to 5 carbon atoms which may be substituted one or more times by alkyl radicals containing up to 6 carbon atoms; and the salts thereof.

The new compounds according to the present invention can be produced by one of the following methods:

a) The reaction of benzene-sulphonyl compounds of the general formula:—



with compounds of the general formula:—

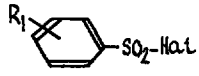


In these two formulae, R_1 and Z have the same meanings as above and one of X and Y is an amino group, while the other is an isocyanate group or a group convertible into an isocyanate group under the reaction conditions.

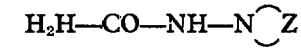
Thus, for example, a sulphonamide (preferably in the form of the sodium or potassium salt) is reacted with a cycloalkylene-imino-isocyanate or, in reversal of this reaction, a sulphonyl isocyanate is condensed with a cycloalkylene hydrazine or an acyl derivative thereof. Instead of the isocyanates, compounds can hereby be used which are capable of conversion into an isocyanic acid ester under the reaction conditions. As "isocyanate formers" of this type, there may be used, for example, on the one hand, carbamic acid halides, urethanes, thiourethanes, ureas, as well as their acyl derivatives, and disulphonyl ureas and, on the other hand, chiefly semicarbazides.

b) The reaction of benzene-sulphonyl halides of the general formula:—

[*Price 4s. 6d.*]



with semicarbazides of the general formula:—



In the above formulae, R_1 and Z have the same meanings as above and Hal is a halogen atom.

In the case of this method, it is preferable to use the corresponding parabanic acid derivatives instead of the alkylene semicarbazides.

The following Examples are given for the purpose of illustrating the present invention:—

EXAMPLE 1

24.9 g N - (*p* - chlorobenzene - sulphonyl)-methyl urethane are heated for 25 minutes at 130°C. with 8.6 g. N-amino-pyrrolidine. The solid reaction product is dissolved in dilute ammonia solution, the solution clarified with charcoal and the filtrate acidified with dilute acetic acid. After filtering off with suction, washing with water and drying, almost pure 4 - (*p* - chlorobenzene - sulphonyl) - 1,1-tetramethylene - semicarbazide is obtained in very good yields. After recrystallisation from methyl glycol, the melting point is 205—207°C. (decomp.)

In an analogous manner, using N-amino-piperidine, there is obtained 4 - (*p* - chlorobenzene - sulphonyl) - 1,1 - pentamethylene-semicarbazide which, after recrystallisation from methanol/dimethyl formamide, melts at 213—214°C.

EXAMPLE 2

23.3 g. N - (*p* - fluorobenzene - sulphonyl)-methyl urethane are suspended in 50 ml. xylene and heated to 90°C., with stirring, whereby the urethane goes into solution. 10.5 g. N-amino-piperidine are added dropwise and the temperature is increased to 110°C. The methanol formed by the reaction is distilled off. The reaction mixture is subsequently heated for 30 minutes at an external temperature of 140°C. After cooling, the fine needles of the precipitated semicarbazide formed are filtered off with suction and washed with methanol and ether. After recrystallisation from dimethyl formamide, the melting point of the 4 - (*p* - fluorobenzene - sulphonyl)-1,1 - pentamethylene - semicarbazide formed is 190—192°C.

In an analogous manner, using N-amino-pyrrolidine, there is obtained 4 - (*p* - fluorobenzene - sulphonyl) - 1,1 - tetramethylene-semicarbazide which, after recrystallisation from dimethyl formamide, melts at 175—177°C.

EXAMPLE 3

A suspension of 29.4 g. N - (*p* - bromobenzene - sulphonyl) - methyl urethane (0.1 mol) in 230 ml. absolute toluene is stirred with 10 g. N-amino-piperidine for 30 minutes at room temperature. The reaction mixture is hereupon heated to boiling, with stirring, on an oil bath for 1¼ hours. From the clear reaction solution there is obtained, upon cooling, 4 - (*p* - bromobenzene - sulphonyl) - 1,1-pentamethylene - semicarbazide. After washing with methanol, it has a melting point of 227—230°C. Yield: 30 g. (83% of theory).

In an analogous manner, by reaction with N-amino-pyrrolidine, there is obtained 4-(*p*-bromobenzene - sulphonyl) - 1,1 - tetramethylene - semicarbazide (m.p. 219°C.).

EXAMPLE 4

By the reaction of nuclear-halogenated benzene-sulphonyl urethanes with methylated N-amino-pyrrolidines and N-amino-piperidines, with stoichiometrical modification of the conditions given in the previous Examples, there can be obtained the following semicarbazides:

4 - (*p* - chlorobenzene - sulphonyl) - 1,1-(α - methyl - pentamethylene) - semicarbazide (m.p. 214—216°C.)

4 - (*p* - chlorobenzene - sulphonyl) - 1,1-(β - methyl - pentamethylene) - semicarbazide (m.p. 223—225°C.)

4 - (*p* - chlorobenzene - sulphonyl) - 1,1-(γ - methyl - pentamethylene) - semicarbazide (m.p. 223—225°C.)

4 - (*p* - chlorobenzene - sulphonyl) - 1,1-(α,α - dimethyl - pentamethylene) - semicarbazide (m.p. 208—210°C.)

4 - (*p* - chlorobenzene - sulphonyl) - 1,1-(α,α - dimethyl - tetramethylene) - semicarbazide (205—208°C.)

4 - (*p* - chlorobenzene - sulphonyl) - 1,1-(β - methyl - tetramethylene) - semicarbazide (m.p. 184°C.)

4 - (*p* - bromobenzene - sulphonyl) - 1,1-(γ - methyl - pentamethylene) - semicarbazide (m.p. 237°C.)

EXAMPLE 5

12.5 g. 4-chlorobenzene-sulphonyl-methyl urethane are heated in a oil bath at 100°C. with 5 g. N-amino-α,α-dimethyl-azetidine. A clear melt is formed which later becomes semi-solid. The reaction product is recrystallised from ethanol/water to give 4 - (*p* - chlorobenzene - sulphonyl) - 1,1 - (α,α - dimethyl-trimethylene) - semicarbazide of melting point 175—176°C.

EXAMPLE 6

9.9 g. *p*-fluorobenzene-sulphonamide sodium salt and 7.2 g. 1,1-pentamethylene-semicarbazide are mixed together in a mortar. The mixture is subsequently heated for 3 hours at 130°C., ammonia is evolved. The reaction product is dissolved in a 1% solution of ammonia and the solution clarified with char-

coal. After acidification of the filtrate, 4 - (*p*-fluorobenzene - sulphonyl) - 1,1 - pentamethylene - semicarbazide precipitates out and, after recrystallsation from dimethyl formamide, it melts at 190—192°C.

EXAMPLE 7

7.8 g. *p*-chlorobenzene-sulphonyl-urea, 120 ml. dioxan and 7.8 g. N-amino-piperidine are heated to boiling under reflux for 1 hour. The solvent is removed in a vacuum, the residue treated with a 1% solution of ammonia and the solution obtained clarified with charcoal. After acidification with acetic acid, there precipitates out from the filtrate 4 -(*p* - chlorobenzene - sulphonyl) - 1,1 - pentamethylene-semicarbazide. After reprecipitation from ammoniacal solution with acetic acid and recrystallisation from ethanol, the substance melts at 213—214°C.

EXAMPLE 8

23 g. N-amino-piperidine are poured over 7.53 g. N - (*p* - chlorobenzene - sulphonyl)-N^1 - acetyl - urea. Salt formation occurs with the evolution of heat. The salt obtained is heated in an oil bath at 130°C. After a few minutes, a clear melt is obtained which, after a further 20 minutes, solidifies. The reaction cake obtained is treated with a 1% solution of ammonia. Undissolved components are filtered off and the filtrate acidified with acetic acid. The 4 - (*p* - chlorobenzene - sulphonyl) - 1,1-pentamethylene - semicarbazide obtained, after again precipitating from ammoniacal solution with acetic acid and recrystallisation from ethanol, melts at 213—214°C.

EXAMPLE 9

9.85 g. 1 - (pentamethylene - imino) - parabanic acid (m.p. 191—193°C.; obtained from 1,1-pentamethylene-semicarbazide by introduction into an excess of oxalyl chloride, heating briefly and distilling off the excess oxalyl chloride, as well as recrystallising from water) are suspended in 125 ml. absolute benzene. There are then added 5 g. triethylamine and, subsequently, 10.5 g. *p* - chlorobenzene - sulphonyl chloride, dissolved in 125 ml. benzene. After boiling under reflux for two hours, the separated triethylamine hydrochloride is filtered off and the filtrate brought to dryness in a vacuum. (By dissolving in isopropanol and adding diisopropyl ether, the parabanic acid derivative can be crystallised; m.p. 178—180°C.) There are then poured over 160 ml. N sodium hydroxide solution and the reaction mixture heated for 10 minutes on a steam bath. After filtration, the filtrate is acidified with acetic acid. The precipitate is purified by reprecipitation from an ammoniacal solution with acetic acid. After recrystallisation from ethanol, with the addition of dimethyl formamide, the 4 - (*p* - chlorobenzene - sulphonyl)-1,1 - pentamethylene - semicarbazide obtained melts at 213—214°C.

EXAMPLE 10

A solution of 7.25 g. N-(*m*-chlorobenzene-sulphonyl)-methyl-urethane and 2.5 g. N-amino-pyrrolidine in 40 cc. absolute toluene is heated under reflux for 3 hours. After cooling, there crystallises out from the reaction solution 4 - (*m* - chlorobenzene - sulphonyl)-1,1 - tetramethylene - semicarbazide which, after reprecipitation from an ammoniacal solution, has a melting point of 167—169°C.

In an analogous manner, there are obtained 4 - (*o* - chlorobenzene - sulphonyl) - 1,1-tetramethylene) - semicarbazide (m.p. 183°C.), 4 - (*o* - chlorobenzene - sulphonyl) - 1,1-(α,α - dimethyl - pentamethylene) - semicarbazide (m.p. 203°C.), 4 - (*m* - chlorobenzene - sulphonyl) - 1,1 - pentamethylene-semicarbazide (m.p. 169°C.) and 4 - (*p*-bromo - benzene - sulphonyl) - 1,1 - (α,α-dimethyl - pentamethylene) - semicarbazide (m.p. 218—219°C.).

EXAMPLE 11

The following salts of 4-(*p*-chlorobenzene-sulphonyl)-1,1-pentamethylene semicarbazide (see Example 1) have also been prepared:—

monosoduim salt: m.p. 325°C., with dark coloration and decomposition.

monopotassium salt: decomposes at 249—252°C. with dark coloration.

monolithium salt: m.p. 187—191°C., with decomposition.

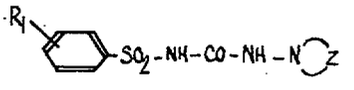
monoammonium salt: decomposes at 164—180°C.

ethylenediamine salt: decomposes at 66—68°C.

diethanolamine salt: decomposes at 112—118°C.

WHAT WE CLAIM IS:—

1. Benzene-sulphonyl-semicarbazides of the general formula:—



wherein R_1 is a halogen atom and Z is an alkylene radical containing 3 to 5 carbon atoms which may be substituted one or more times by alkyl radicals containing up to 6 carbon atoms; and the salts thereof.

2. 4 - (*p* - chlorobenzene - sulphonyl) - 1,1-tetramethylene - semicarbazide.

3. 4 - (*p* - chlorobenzene - sulphonyl) - 1,1-pentamethylene - semicarbazide.

4. 4 - (*p* - fluorobenzene - sulphonyl) - 1,1-pentamethylene - semicarbazide.

5. 4 - (*p* - fluorobenzene - sulphonyl) - 1,1-tetramethylene - semicarbazide.

6. 4 - (*p* - bromobenzene - sulphonyl) - 1,1-pentamethylene - semicarbazide.

7. 4 - (*p* - bromobenzene - sulphonyl) - 1,1-tetramethylene - semicarbazide.

coal. After acidification of the filtrate, 4 - (*p*-fluorobenzene - sulphonyl) - 1,1 - pentamethylene - semicarbazide precipitates out and, after recrystallisation from dimethyl formamide, it melts at 190—192°C.

EXAMPLE 7

7.8 g. *p*-chlorobenzene-sulphonyl-urea, 120 ml. dioxan and 7.8 g. N-amino-piperidine are heated to boiling under reflux for 1 hour. The solvent is removed in a vacuum, the residue treated with a 1% solution of ammonia and the solution obtained clarified with charcoal. After acidification with acetic acid, there precipitates out from the filtrate 4 -(*p* - chlorobenzene - sulphonyl) - 1,1 - pentamethylene-semicarbazide. After reprecipitation from ammoniacal solution with acetic acid and recrystallisation from ethanol, the substance melts at 213—214°C.

EXAMPLE 8

23 g. N-amino-piperidine are poured over 7.53 g. N - (*p* - chlorobenzene - sulphonyl)-N^1 - acetyl - urea. Salt formation occurs with the evolution of heat. The salt obtained is heated in an oil bath at 130°C. After a few minutes, a clear melt is obtained which, after a further 20 minutes, solidifies. The reaction cake obtained is treated with a 1% solution of ammonia. Undissolved components are filtered off and the filtrate acidified with acetic acid. The 4 - (*p* - chlorobenzene - sulphonyl) - 1,1-pentamethylene - semicarbazide obtained, after again precipitating from ammoniacal solution with acetic acid and recrystallisation from ethanol, melts at 213—214°C.

EXAMPLE 9

9.85 g. 1 - (pentamethylene - imino) - parabanic acid (m.p. 191—193°C.; obtained from 1,1-pentamethylene-semicarbazide by introduction into an excess of oxalyl chloride, heating briefly and distilling off the excess oxalyl chloride, as well as recrystallising from water) are suspended in 125 ml. absolute benzene. There are then added 5 g. triethylamine and, subsequently, 10.5 g. *p* - chlorobenzene - sulphonyl chloride, dissolved in 125 ml. benzene. After boiling under reflux for two hours, the separated triethylamine hydrochloride is filtered off and the filtrate brought to dryness in a vacuum. (By dissolving in isopropanol and adding diisopropyl ether, the parabanic acid derivative can be crystallised; m.p. 178—180°C.) There are then poured over 160 ml. N sodium hydroxide solution and the reaction mixture heated for 10 minutes on a steam bath. After filtration, the filtrate is acidified with acetic acid. The precipitate is purified by reprecipitation from an ammoniacal solution with acetic acid. After recrystallisation from ethanol, with the addition of dimethyl formamide, the 4 - (*p* - chlorobenzene - sulphonyl)-1,1 - pentamethylene - semicarbazide obtained melts at 213—214°C.

EXAMPLE 10

A solution of 7.25 g. N-(*m*-chlorobenzene-sulphonyl)-methyl-urethane and 2.5 g. N-amino-pyrrolidine in 40 cc. absolute toluene is heated under reflux for 3 hours. After cooling, there crystallises out from the reaction solution 4 - (*m* - chlorobenzene - sulphonyl)-1,1 - tetramethylene - semicarbazide which, after reprecipitation from an ammoniacal solution, has a melting point of 167—169°C.

In an analogous manner, there are obtained 4 - (*o* - chlorobenzene - sulphonyl) - 1,1-tetramethylene) - semicarbazide (m.p. 183°C.), 4 - (*o* - chlorobenzene - sulphonyl) - 1,1-(α,α - dimethyl - pentamethylene) - semicarbazide (m.p. 203°C.), 4 - (*m* - chlorobenzene - sulphonyl) - 1,1 - pentamethylene-semicarbazide (m.p. 169°C.) and 4 - (*p*-bromo - benzene - sulphonyl) - 1,1 - (α,α-dimethyl - pentamethylene) - semicarbazide (m.p. 218—219°C.).

EXAMPLE 11

The following salts of 4-(*p*-chlorobenzene-sulphonyl)-1,1-pentamethylene semicarbazide (see Example 1) have also been prepared:—

monosoduim salt: m.p. 325°C., with dark coloration and decomposition.

monopotassium salt: decomposes at 249—252°C. with dark coloration.

monolithium salt: m.p. 187—191°C., with decomposition.

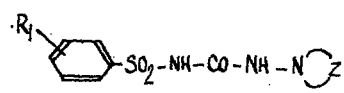
monoammonium salt: decomposes at 164—180°C.

ethylenediamine salt: decomposes at 66—68°C.

diethanolamine salt: decomposes at 112—118°C.

WHAT WE CLAIM IS:—

1. Benzene-sulphonyl-semicarbazides of the general formula:—



wherein R_1 is a halogen atom and Z is an alkylene radical containing 3 to 5 carbon atoms which may be substituted one or more times by alkyl radicals containing up to 6 carbon atoms; and the salts thereof.

2. 4 - (*p* - chlorobenzene - sulphonyl) - 1,1-tetramethylene - semicarbazide.

3. 4 - (*p* - chlorobenzene - sulphonyl) - 1,1-pentamethylene - semicarbazide.

4. 4 - (*p* - fluorobenzene - sulphonyl) - 1,1-pentamethylene - semicarbazide.

5. 4 - (*p* - fluorobenzene - sulphonyl) - 1,1-tetramethylene - semicarbazide.

6. 4 - (*p* - bromobenzene - sulphonyl) - 1,1-pentamethylene - semicarbazide.

7. 4 - (*p* - bromobenzene - sulphonyl) - 1,1-tetramethylene - semicarbazide.

8. 4 - (*p* - chlorobenzene - sulphonyl) - 1,1- (*α* - methyl - pentamethylene) - semicarbazide.

9. 4 - (*p* - chlorobenzene - sulphonyl) - 1,1- (*β* - methyl - pentamethylene) - semicarbazide.

10. 4 - (*p* - chlorobenzene - sulphonyl)- 1,1 - (*γ* - methyl - pentamethylene) - semicarbazide.

11. 4 - (*p* - chlorobenzene - sulphonyl)- 1,1 - (*α*,*α* - dimethyl - pentamethylene) - semicarbazide.

12. 4 - (*p* - chlorobenzene - sulphonyl)- 1,1 - (*α*,*α* - dimethyl - tetramethylene) - semicarbazide.

13. 4 - (*p* - chlorobenzene - sulphonyl) - 1,1- (*β* - methyl - tetramethylene) - semicarbazide.

14. 4 - (*p* - bromobenzene - sulphonyl) - 1,1- (*γ* - methyl - ~~pantamethylene~~ pentamethylene) - semicarbazide.

15. 4 - (*p* - chlorobenzene - sulphonyl) - 1,1- (*α*,*α* - dimethyl - trimethylene) - semicarbazide.

16. 4 - (*m* - chlorobenzene - sulphonyl)- 1,1 - tetramethylene - semicarbazide.

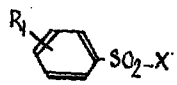
17. 4 - (*o* - chlorobenzene - sulphonyl) - 1,1- tetramethylene - semicarbazide.

18. 4 - (*o* - chlorobenzene - sulphonyl) 1,1- (*α*,*α* - dimethyl - pentamethylene) - semicarbazide.

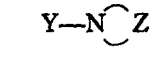
19. 4 - (*m* - chlorobenzene - sulphonyl) - 1,1- pentamethylene - semicarbazide.

20. 4 - (*p* - bromobenzene - sulphonyl) - 1,1- (*α*,*α* - dimethyl - pentamethylene) - semicarbazide.

21. Process for the production of benzene-sulphonyl-semicarbazides of the general formula given in claim 1, wherein a benzene-sulphonyl compound of the general formula: —

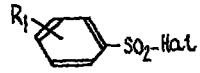


is reacted with a compound of the general formula: —

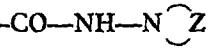


in which R_1 and Z have the same meanings as above and one of X and Y is an amino group and the other is an isocyanate group or a group which is converted into an isocyanate group under the reaction conditions.

22. Process for the production of benzene-sulphonyl semicarbazides of the general formula given in claim 1, wherein a benzene-sulphonyl halide of the general formula: —



in which R_1 has the same meaning as above and Hal is a halogen atom, is reacted with a semicarbazide of the general formula: —



in which Z has the same meaning as above, or with the corresponding parabanic acid derivative.

23. Process for the production of benzene sulphonyl semicarbazides of the general formula given in claim 1, substantially as hereinbefore described and with reference to any of the specific Examples.

24. Benzene-sulphonyl semicarbazides of the general formula given in claim 1, whenever prepared by the process according to any of claims 21 to 23.

For the Applicants,
CARPMAELS & RANSFORD,
Chartered Patent Agents,
24 Southampton Buildings, Chancery Lane,
London, W.C.2.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press (Leamington) Ltd.—1964. Published by The Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.

* C L M S *