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PATENT SPECIFICATION

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COMPLETE SPECIFICATION

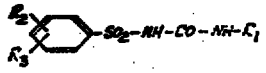
Manufacture of New Sulphonyl-Ureas

We, FARBWERKE HOECHST AKTIENGESELLSCHAFT, vormals Meister Lucius & Brüning, a body corporate recognised under German Law, of Frankfurt (M)-Hoechst, 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:—

It is known from literature that certain compounds belonging to the class of aminobenzene sulphonamides are capable of lowering the blood sugar value in test animals, for example, of dogs. Thus, for example, para-aminobenzene - sulphonamido-isopropyl-thiadiazole produces a moderate lowering of the blood sugar value in dogs for 4 to 6 hours (compare: Jean La Barre and Jean Reuse, Arch. Neerland physiol. *28* [1947] page 475). These compounds, however have a bacteriostatic action, and have not been proposed as being suitable for the treatment of diabetes mellitus in human beings.

There are also known certain benzene-sulphonyl ureas, such as N-benzenesulphonyl-urea, N-benzenesulphonyl-N¹-phenyl-urea, N-benzenesulphonyl-N¹:N¹-diethyl-urea, N-para-toluenesulphonyl-urea and N-para-toluene-sulphonyl-N¹-phenyl-urea (compare: Chem. Rev., volume 50, pages 28/29). These substances have not yet attained any commercial importance, and have found no application in lowering the blood sugar level in the treatment of diabetes mellitus.

The present invention provides sulphonyl-ureas of the general formula

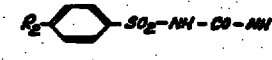


in which R_1 represents an aliphatic or cycloaliphatic hydrocarbon radical containing from 2 to 8 carbon atoms, R_2 represents a chlorine or bromine atom and R_3 represents a hydrogen, chlorine or bromine atom or an alkyl or alkoxy group containing at most 6 carbon atoms; and salts of such compounds with bases yielding physiologically tolerable salts with the compounds.

The residue



may be, for example, a chlorophenyl, bromophenyl or a phenyl residue that contains both an alkyl or alkoxy group and a bromine or chlorine atom, such as a methyl-chlorophenyl group. The substituents may be bound in any desired position in the benzene nucleus. R_1 may be, for example, an ethyl, propyl, allyl, butyl, butenyl, pentyl, hexyl, cyclohexyl or hexahydrobenzyl group. The aliphatic residues may have straight or branched chains. Among the compounds of the above general formula there may be mentioned more especially those in which R_1 represents an aliphatic or cycloaliphatic hydrocarbon radical containing from 3 to 5 carbon atoms; also compounds of the general formula



in which R_2 represents chlorine or bromine and R_3 represents an aliphatic or cycloaliphatic radical containing 2 to 8, especially 3 to 5, carbon atoms.

The compounds of the above general

[Price 3s. 6d.]

formula may be made by methods in themselves known for making sulphonyl-ureas. As examples the following processes may be mentioned:

A chloro-benzene-sulphonyl isocyanate which may be mono-alkylated or alkoxylated, may be reacted with a primary butyl-amine or another primary alkylamine or an alkenylamine, cyclo-alkylamine or cycloalkyl-alkylamine containing 2 to 8 carbon atoms. Conversely, the desired sulphonyl-urea can be made by reacting a butyl isocyanate or other appropriate isocyanate with a chloro-benzene-sulphonamide, which may be mono-alkylated or alkoxylated, advantageously in the form of a salt thereof. Instead of isocyanates there may be used compounds convertible into isocyanates in the course of the reaction, such as acid azides, for example, valeric acid azide. In another process for making the new compounds there are used, instead of isocyanates, urethanes and any desired carbamic acid ester, such as methyl, ethyl, propyl, butyl or aryl esters, can be used for this purpose. For example, a chloro-benzene sulphonyl-urethane, which may be mono-alkylated or alkoxylated in the benzene nucleus, may be reacted, for example, with butylamine or another primary amine, or, conversely, an alkyl-urethane may be reacted with an appropriate benzene-sulphonamide, advantageously in the form of a salt thereof. Carbamic acid halides can also be used with special advantage. Thus, for example, the new sulphonyl-ureas are formed by reacting a butylcarbamic acid chloride with a chloro-benzene sulphonamide, which may be mono-alkylated or alkoxylated, or by reacting a similarly substituted benzene sulphonyl-carbamic acid chloride with a butylamine or another primary amine. In a further process a chloro-benzene sulphonyl-urea, which is unsubstituted in the $-NH_2$ group, is converted into a chloro-benzene sulphonyl-alkyl-urea for example, with butylamine. Alternatively, an alkyl-urea may be reacted with a chloro-benzene-sulphonamide. Instead of the alkyl-ureas other derivatives may be used. Furthermore, instead of the alkyl-ureas there may be used the corresponding iso-urea ethers, advantageously in the form of their salts, and they are reacted with chloro-benzene sulphonic acid chlorides, and the product so obtained is then converted by hydrolysis into the desired sulphonyl-urea.

In further processes for making the new compounds the corresponding thiourea is first prepared, and sulphur is eliminated therefrom in a conventional manner; or an N-chloro-benzene sulphonyl -N'-alkyl-guanidine is prepared in known manner (for example, by reacting chloro-benzenesulphonyl-cyanamide with a butylamine or with another primary amine), and the resulting guanidine is then hydrolysed.

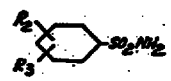
In all cases the benzene residue may contain instead of a chlorine atom a bromine atom and may also be substituted by a single alkyl or alkoxy group containing up to 6 carbon atoms or by a further chlorine or bromine atom. Instead of butylamine, another primary alkylamine, or an alkenylamine, cycloalkylamine or cycloalkyl-alkyl-amine may be used. In these reactions the components must be so chosen that the radical R_1 in the product contains 2 to 8 carbon atoms, especially 3 to 5 carbon atoms.

As alkyl or alkoxy residues, of which one may be present as substituent in the phenyl radical in addition to the chlorine or bromine atom, there are used those containing 1 to 6 carbon atoms. If residues of higher molecular weight are used the activity of the products is generally considerably lower.

The primary amines used as starting materials in the above processes advantageously contain saturated or unsaturated aliphatic or cycloaliphatic hydrocarbon radicals containing 2 to 6 carbon atoms. However, they may contain radicals of higher molecular weight, but radicals containing more than 8 carbon atoms generally reduce the activity of the products.

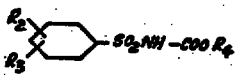
The reaction conditions under which the aforesaid processes are carried out may vary within wide limits and are adapted to each particular case. For example, the reactions may be carried out with the use of solvents at room temperature or at a higher temperature. Particularly suitable are the following processes:

(1) The reaction of a compound



in which R_2 and R_3 have the meanings given above, and advantageously in the form of an alkali metal salt, with an isocyanate of the general formula $R_1—NCO$ in which R_1 has the meaning given above, in the presence of a solvent, for example, nitrobenzene or acetone, at the ordinary or a higher temperature.

(2) The reaction of a benzene sulphonyl-carbamic acid ester of the general formula



in which R_2 and R_3 have the meaning given above, and R_4 represents any desired, preferably lower, hydrocarbon residue, with an equivalent quantity of an amine of the formula $R_1—NH_2$. In this case it is advantageous to conduct the reaction at a temperature within the range of 100° C to 140° C.

To obtain the products in as pure a state as possible, it is advantageous to separate the

product thoroughly from the substituted benzene sulphonamide used as starting material or formed in the course of the reaction. Advantageously, this is carried out by taking up the product in dilute ammonia (1 part by volume of ammonia to 20—30 parts by volume of water), since the sulphonamides are generally sparingly soluble in this medium at room temperature.

Many of the starting materials suitable for use in the present process have been described in the literature. As starting materials there may be mentioned, for example, chloro- or bromo-benzenesulphonyl isocyanates, in which the halogen atom may be in any desired position in the benzene nucleus; correspondingly substituted benzenesulphonamides; correspondingly substituted benzenesulphonyl-urethanes containing in the urethane component a lower alkyl radical, for example, a methyl, ethyl, propyl or butyl group, and more especially an ethyl group, or an aryl radical; correspondingly substituted benzenesulphonyl-ureas; and correspondingly substituted benzene sulphonic acid halides.

Furthermore there may be used as starting materials; dichloro- or dibromo-benzene-sulphonyl isocyanates, of which the halogen atoms may be in any desired positions of the benzene nucleus; correspondingly disubstituted benzene sulphonamides; correspondingly disubstituted benzene-sulphonyl-urethanes containing in the urethane component a lower alkyl radical, for example, a methyl, propyl, butyl or especially an ethyl group, or an aryl residue; correspondingly disubstituted benzene-sulphonyl-ureas; correspondingly disubstituted benzene-sulphonic acid halides; and correspondingly disubstituted benzene-sulphonyl carbamic acid halides. There may also be used as starting materials methyl-chlorobenzene-, methyl-bromobenzene-, methoxy-chlorobenzene- and methoxy-bromobenzene-sulphonyl compounds in the form of the chlorides, amides, isocyanates, carbamic acid halides, carbamic acid esters or ureas. Instead of the methyl group an ethyl, propyl or butyl group may be present.

For the reaction with the compounds mentioned above there may be used the following primary amines: As alkylamines there may be mentioned, for example, ethylamine, *n*-propylamine, isopropylamine, *n*-butylamine, isobutylamine, secondary butylamine, tertiary butylamine pentylamine-(1), pentylamine-(2), pentylamine-(3), 3-methylbutylamine-(1)-, 2-methyl-butylamine-(1), 2:2-dimethyl-propylamine-(1), 3-methyl-butylamine-(2) hexylamines such as hexylamine-(1) and 2-methyl-pentylamine-(1), heptylamines such as heptylamine-(1) and heptylamine-(4), and octylamines such as octylamine-(1).

There may be mentioned as examples of alkenylamines, allylamines and crotylamine; as cycloalkylamines, cycloalkylamines, cyclohexylamine and cyclopentylamine; and as cycloalkyl-alkylamines, cyclohexyl-methylamine and cyclohexyl-ethylamine.

Instead of using the aforesaid amines, the corresponding isocyanates, urethanes, carbamic acid halides or ureas may be reacted with suitably substituted benzene sulphonamides, or isourea ethers (obtainable from the aforesaid amines) may be reacted with sulphone halides.

When the synthesis of the desired sulphonyl-urea starts from a corresponding thiourea, for example, from N-4-chloro-benzenesulphonyl-N'-alkyl, alkenyl-, -cycloalkyl- or -cycloalkyl-alkyl- thioureas, the hydrocarbon radicals of which contain 2—8 carbon atoms, the sulphur may be eliminated with a heavy metal oxide or a salt thereof, for example, an oxide or salt of lead, copper or silver, in an aqueous or alcoholic solution.

Alternatively, the desired sulphonyl-urea can be prepared by hydrolysing an appropriately constituted guanidine with an alkaline solution.

The products may be used as such or in the form of their salts, or in the presence of substances that cause salt formation. For salt formation there are used bases which yield physiologically tolerated salts with the compounds, for example, ammonia, an alkaline substance such as an alkali metal or alkaline earth metal hydroxide, an alkali metal carbonate or bicarbonate, or a suitable organic base. The compounds can be made up, inter alia, into preparations suitable for oral administration and lowering the blood sugar in the treatment of diabetes.

As is well known and practised in the art such preparations may comprise tablets, pills, capsules, cachets, mixtures, solutions or powders. The compounds are preferably made up in admixture or conjunction with an adjuvant facilitating the administration of the compound, for example, in admixture with a pharmaceutical organic or inorganic carrier material suitable for oral administration.

The pharmaceutical preparations can be made up enveloping a suitable dosage quantity, for example, 0.5 grams, of the sulphonyl urea compound: and it is to be understood that the present invention includes such preparations which comprise a sulphonyl-urea compound or salt thereof, in accordance with the invention in admixture or conjunction with a pharmaceutically suitable carrier.

In animal tests the action on the blood sugar level has been demonstrated, for example, on mice-, rats, rabbits, and dogs. When for instance, a compound of the invention (as specified in Table 1 below) is administered to normally fed rabbits in a single average dose of 400 mg/kg in, for example, a solution rendered alkaline with bicarbonate, or in the form of an alkali metal salt, a lowering of the blood sugar level sets in rapidly and reaches a maximum (about 30 to 40 per cent of the initial value) in the course of about 3 to 4 hours.

The blood sugar level can be measured by hourly analyses by the method of Hagedorn-Jensen. The lowering of the blood sugar is determined by comparison with the blood-sugar level of control animals fed in the same way but not so treated.

The activity of some of the products of the inventions is shown in the following Table:

TABLE I

SUBSTANCE (in the form of the sodium salt)	maximum lowering of blood sugar in the rabbit; dose: 400 mg/kg per os.
N - (4 - chloro-benzenesulphonyl)-N¹-*n*-butyl-urea	30%
N - (3 - chloro-benzenesulphonyl)-N¹-*n*-butyl-urea	50%
N - (3 - chloro - 4 - methyl-benzenesulphonyl)-N¹-isobutyl-urea	30%

The testing of the compounds on dogs has the advantage that the resorption conditions in the alimentary canal are similar to those of human beings, and that the blood sugar level exhibits smaller individual variations than in rabbits. In the canine tests the administration of small doses of even the free sulphonyl-ureas yields readily reproducible values. When the compound N-(4-chloro-benzenesulphonyl)-N¹-butyl-urea is administered to a dog, prior to feeding it, in a single dose of 100 mg/kg, and the blood sugar level is determined at certain intervals, the following reductions in the blood sugar level are observed:—

% lowering of blood sugar level of the dog	After . . . hours
27	1
40	3
40	24
32	48
15	72
0	96

The above values were determined by comparison with the blood sugar levels measured on similarly fed, but untreated control animals.

As compared with compounds of similar constitution of the sulphanilyl series the compounds of the present invention possess the advantage that they have no bacteriostatic action, and do not produce the secondary effects of sulphonamides on the blood (Heinz bodies) or on the thyroid gland, nor the digestive disturbances caused by action of the bacterial flora of the alimentary tract.

French Specification No. 993,465 describes *inter alia* a process for the manufacture of compounds of the general formula

$$R—SO_2—NH—CX—NH—R^1,$$

in which R and R¹ each represent organic residues and X represents oxygen or sulphur, wherein a sulphonamide, for example, a chlorobenzene-sulphonamide, is reacted with a polyisocyanate or polyisothiocyanate, for example, ethyl- or hexyl- isocyanate. It contains, however, no specific example of a compound falling within the general formula of the compounds of the present invention, nor does it disclose or suggest that the compounds are useful for lowering the blood sugar level. In fact, none of the compounds specifically exemplified in the French specification is useful as an anti-diabetic for oral administration.

Specification No. 34857/45, as open to public inspection under Section 91 (4) of the Patents and Designs Acts, 1907—46, describes a process for the manufacture of substituted sulphonyl-ureas of the general formula

$$R_1—SO_2—\underset{\displaystyle R_2}{\underset{|}{N}}—CO—NH—R_3,$$

in which R_1 represents an aromatic or araliphatic residue, R_2 represents hydrogen or an organic residue and R_3 represents an organic residue, which comprises reacting an aromatic or araliphatic N-sulphonyl-urea, for example, benzenesulphonyl - urea or para-toluenesulphonyl-urea, with an amine or salt thereof, especially a primary amine; the specification mentions *inter alia* aliphatic amines as the amine component, but it contains no specific disclosure of the preparation of any of the sulphonyl-urea compounds of the present invention and, moreover, there is no disclosure or suggestion therein that any of the substituted

sulphonyl-ureas are useful for lowering the blood sugar level.

Furthermore, none of the compounds specifically exemplified in Specification No. 34857/45 is useful as an anti-diabetic for oral administration.

The following Examples illustrate the invention:—



Example 1.
N-4-chlorobenzenesulphonyl-N¹-*n*-butyl-urea

95.5 grams of 4-chlorobenzene-sulphonamide are suspended in 500 cc of acetone and dissolved by addition of a solution of 20 grams of sodium hydroxide in 400 cc of water.

The solution is cooled to +10° C, and while stirring vigorously, 49.5 grams of *n*-butyl isocyanate are slowly added dropwise. The reaction mixture is stirred until the odour of isocyanate has disappeared. It is then filtered with suction, about two thirds of the solvent are distilled off, the residue is diluted with water and carefully acidified with acetic acid, while stirring. The precipitate is at first somewhat pasty but becomes crystalline on standing in the cold. The N-4-chlorobenzene-sulphonyl-N¹-*n*-butyl-urea, obtained in a good yield, is purified by being dissolved in dilute ammonia solution. The solution is clarified with charcoal and acidified with dilute acetic acid. The precipitated N-4-chlorobenzene-sulphonyl-N¹-*n*-butyl-urea is filtered off with suction and thoroughly washed with water on the filter. After recrystallisation from dilute ethanol the product melts at 115—116° C.

In an analogous manner there is obtained from 3-chloro-benzene-sulphonamide, N-3-chlorobenzenesulphonyl-N¹-*n*-butyl-urea melting at 111—112° C.

Example 2.
N-4-chlorobenzenesulphonyl-N¹-cyclohexyl-urea

50 grams of finely ground potassium carbonate are added to a solution of 25 grams of 4-chlorobenzene-sulphonamide in 200 cc of dry acetone, and the suspension is refluxed for 3 hours. 16.5 grams of cyclohexyl isocyanate are then slowly added dropwise, while stirring, at 50° C. The mixture is further stirred at the same temperature until the odour of isocyanate is no longer detected. After being cooled, the mixture is filtered with suction, the residue is dissolved in water, any undissolved matter is filtered off, and the solution is decolorised with carbon. The sulphonyl-urea is then precipitated by cautiously adding an acid, then dissolved in dilute ammonia solution, the solution is clarified with carbon and acidified with acetic acid. A good yield of N-4-chlorobenzenesulphonyl-N¹-cyclohexyl-urea precipitates. It is filtered off with suction, thoroughly washed on the filter with water, and recrystallised from acetonitrile. It melts at 158—159° C.

Example 3.
N-4-bromobenzenesulphonyl-N¹-*n*-butyl-urea

A solution of 8 grams of sodium hydroxide in 75 cc of water is added to a solution of 47 grams of 4-bromobenzene-sulphonamide in 150 cc of acetone. While stirring vigorously, 20 grams of *n*-butyl-isocyanate are slowly added dropwise at 20° C to the reaction mixture. When the addition is complete, the mixture is stirred until the odour of isocyanate has disappeared. The reaction mixture is then evaporated, and the residue is dissolved in water. The solution is clarified with carbon and acidified with hydrochloric acid. To purify the precipitated sulphonyl-urea, it is dissolved in dilute ammonia solution, and the solution is clarified with carbon and acidified with acetic acid. N-4-bromobenzenesulphonyl-N¹-*n*-butyl-urea is obtained in good yield. It is filtered off with suction, washed with water and recrystallised from dilute ethanol. It melts at 126—127° C.

Example 4.
N-(4-methyl-3-chlorobenzenesulphonyl)-N¹-(*n*-butyl)-urea

51 grams of 4-methyl-3-chlorobenzene-sulphonamide are suspended in 80 cc of acetone. The suspension is mixed with 150 cc of caustic soda solution containing 10 grams of sodium hydroxide, and, while stirring, 25 grams of *n*-butylisocyanate are added dropwise, the temperature being maintained at about 10° C. The reaction solution is clarified with carbon, filtered, and acidified with dilute acetic acid. A good yield of crystalline N-(4-methyl - 3 - chlorobenzenesulphonyl) - N¹-(*n*-butyl)-urea is obtained. It is recrystallised from dilute ethanol or from isopropanol. It melts at 145—146° C.

In analogous manner there is obtained from 103 grams of 2-methyl-6-chlorobenzene-sulphonamide in 165 cc of acetone and 330 cc of caustic soda solution (containing 20 grams of sodium hydroxide) by reaction with 50 grams of *n*-butyl isocyanate, N-(2-methyl-6-chlorobenzene-sulphonyl) - N¹ - (*n*-butyl)-urea melting at 154—155° C.

Example 5.
N-(4-methyl-3-chlorobenzenesulphonyl)-N¹-isobutyl-urea

(a) A suspension of 64 grams of 4-methyl-3-chlorobenzenesulphonamide, 120 grams of potassium carbonate and 600 cc of acetone is heated, while stirring, for 1 hour at 55° C. 37.6 grams of ethyl chlorocarbonate are then slowly added dropwise, and the whole is stirred for 4 hours at 55° C. After cooling the mixture, the precipitate is filtered off with suction and dissolved in 500 cc of water. The filtrate is clarified with animal charcoal and acidified with hydrochloric acid to precipitate 4-methyl-3-chloro-benzenesulphonyl-carbamic acid ethyl ester in the form of a smeary mass which

soon crystallises throughout. The resulting 4 - methyl - 3 - chlorobenzenesulphonyl-carbamic acid ethyl ester is filtered off with suction and washed with water. The product melts at 85—87° C.

(b) 55.5 grams of the resulting dried 4-methyl - 3 - chlorobenzenesulphonyl - carbamic acid ethyl ester are refluxed at the boil for 4 hours with 16 grams of isobutylamine in 107 grams of glycol monomethyl ether. The mixture is then evaporated under reduced pressure. The warm residue is dissolved in dilute ammonia solution. The solution so obtained is clarified with animal charcoal and a small quantity of 4-methyl-3-chlorobenzene-sulphonamide is removed. Acidification of the filtrate with dilute hydrochloric acid produces a crystalline precipitate of N-(4-methyl-3-chlorobenzene-sulphonyl)-N¹-isobutyl - urea, which is filtered off with suction and recrystallised from aqueous ethanol of 75 per cent strength. The product melts at 157—159° C.

EXAMPLE 6.

(I) 50 kg of N-(4-chlorobenzenesulphonyl)-N¹-*n*-butyl-urea, 2.95 kg of wheat or maize starch, 0.75 kg of talcum and 0.3 kg of magnesium stearate were well mixed and kneaded for a short while (about 15 minutes) in a Werner-Pfleiderer type kneader with 1 kg of wheat or maize starch as a starch paste which has been prepared by heating with 6 litres of distilled water on a water bath. The moist mass was passed through a sieve having meshes of 2 mm in diameter, then collected on 20 drying plates, and dried for 12 hours at 40° C in a circulating air drying chamber. The dry mass was again passed through a sieve having meshes 1.2 mm in diameter.

(II) 10 kg of wheat or maize starch were moistened with distilled water and kneaded in a Werner-Pfleiderer type kneader. The moist starch was passed through a sieve having meshes 0.75 mm in diameter, collected in not too thick a layer on aluminium plates, and dried for 12 hours at 40° C in an air-circulating drying chamber.

(III) Granulate I and granulate II were mixed with one another in a ratio of 50 parts by weight (I) to 10 parts by weight of (II).

(IV) The uniform mixture III was tabletted on a rotating press.

Composition of one tablet:

Dosage per tablet: 0.5 gram of N-(4-chloro-benzenesulphonyl)-N¹-*n*-butyl-urea.

Final weight per tablet: 0.650 grams.

Diameter per tablet: 13 mm.

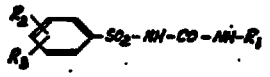
Column Height of 10 tablets: 45 mm.

Depth of curvature of seal: 0.3 mm.

Instead of N-(4-chloro-benzenesulphonyl)-N¹-*n*-butyl urea there may be used in the above preparation N - (3-chloro-benzenesulphonyl)-N¹-*n*-butyl urea or N-(3-chloro-4-methyl-benzenesulphonyl)-N¹-isobutyl urea.

WHAT WE CLAIM IS:—

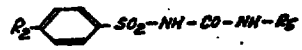
1. Compounds of the general formula



in which R_1 represents an aliphatic or cycloaliphatic hydrocarbon radical containing from 2 to 8 carbon atoms, R_2 represents a chlorine or bromine atom and R_3 represents a hydrogen, chlorine or bromine atom or an alkyl or alkoxy group containing at most 6 carbon atoms.

2. Compounds of the general formula given in claim 1, wherein R_1 represents an aliphatic or cycloaliphatic hydrocarbon radical containing from 3 to 5 carbon atoms.

3. Compounds of the general formula



in which R_2 represents chlorine or bromine and R_5 represents an aliphatic or cycloaliphatic hydrocarbon radical containing 2 to 8, especially 3 to 5, carbon atoms.

4. N - 4 - Chlorobenzenesulphonyl - N¹-*n*-butyl-urea.

5. N - 4 - Chlorobenzenesulphonyl - N¹-cyclohexyl-urea.

6. N - 4 - Bromobenzenesulphonyl - N¹-*n*-butyl-urea.

7. N-(4-Methyl-3-Chlorobenzenesulphonyl)-N¹-(*n*-butyl)-urea.

8. N-(4-Methyl-3-Chlorobenzenesulphonyl)-N¹-isobutyl-urea.

9. Salts of any one of the compounds claimed in any one of claims 1—8, with bases yielding physiologically tolerable salts with such compound.

10. A process for the manufacture of a compound claimed in any one of claims 1—8, conducted substantially as hereinbefore described.

11. A preparation for oral administration and lowering the blood sugar level in the treatment of diabetes mellitus which comprises a compound as claimed in claim 1 in admixture or conjunction with a pharmaceutically suitable carrier.

12. A preparation for oral administration and lowering the blood sugar level in the treatment of diabetes mellitus, which comprises a compound as claimed in any one of claims 2 to 8 in admixture or conjunction with a pharmaceutically suitable carrier.

13. A preparation for oral administration and lowering the blood sugar level in the treatment of diabetes mellitus, which comprises a salt of a compound as claimed in claim 1 with a base yielding a physiologically tolerable salt with such compound in admixture or con-

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soon crystallises throughout. The resulting 4 - methyl - 3 - chlorobenzenesulphonylcarbamic acid ethyl ester is filtered off with suction and washed with water. The product melts at 85—87° C.

(b) 55.5 grams of the resulting dried 4-methyl - 3 - chlorobenzenesulphonyl - carbamic acid ethyl ester are refluxed at the boil for 4 hours with 16 grams of isobutylamine in 107 grams of glycol monomethyl ether. The mixture is then evaporated under reduced pressure. The warm residue is dissolved in dilute ammonia solution. The solution so obtained is clarified with animal charcoal and a small quantity of 4-methyl-3-chlorobenzene-sulphonamide is removed. Acidification of the filtrate with dilute hydrochloric acid produces a crystalline precipitate of N-(4-methyl-3-chlorobenzene-sulphonyl)-N¹-isobutyl - urea, which is filtered off with suction and recrystallised from aqueous ethanol of 75 per cent strength. The product melts at 157—159° C.

EXAMPLE 6.

(I) 50 kg of N-(4-chlorobenzenesulphonyl)-N¹-*n*-butyl-urea, 2.95 kg of wheat or maize starch, 0.75 kg of talcum and 0.3 kg of magnesium stearate were well mixed and kneaded for a short while (about 15 minutes) in a Werner-Pfleiderer type kneader with 1 kg of wheat or maize starch as a starch paste which has been prepared by heating with 6 litres of distilled water on a water bath. The moist mass was passed through a sieve having meshes of 2 mm in diameter, then collected on 20 drying plates, and dried for 12 hours at 40° C in a circulating air drying chamber. The dry mass was again passed through a sieve having meshes 1.2 mm in diameter.

(II) 10 kg of wheat or maize starch were moistened with distilled water and kneaded in a Werner-Pfleiderer type kneader. The moist starch was passed through a sieve having meshes 0.75 mm in diameter, collected in not too thick a layer on aluminium plates, and dried for 12 hours at 40° C in an air-circulating drying chamber.

(III) Granulate I and granulate II were mixed with one another in a ratio of 50 parts by weight (I) to 10 parts by weight of (II).

(IV) The uniform mixture III was tabletted on a rotating press.

Composition of one tablet:

Dosage per tablet: 0.5 gram of N-(4-chloro-benzenesulphonyl)-N¹-*n*-butyl-urea.

Final weight per tablet: 0.650 grams.

Diameter per tablet: 13 mm.

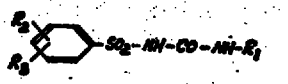
Column Height of 10 tablets: 45 mm.

Depth of curvature of seal: 0.3 mm.

Instead of N-(4-chloro-benzenesulphonyl)-N¹-*n*-butyl urea there may be used in the above preparation N - (3-chloro-benzenesulphonyl)-N¹-*n*-butyl urea or N-(3-chloro-4-methyl-benzenesulphonyl)-N¹-isobutyl urea.

WHAT WE CLAIM IS:—

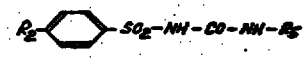
1. Compounds of the general formula



in which R_1 represents an aliphatic or cycloaliphatic hydrocarbon radical containing from 2 to 8 carbon atoms, R_2 represents a chlorine or bromine atom and R_3 represents a hydrogen, chlorine or bromine atom or an alkyl or alkoxy group containing at most 6 carbon atoms.

2. Compounds of the general formula given in claim 1, wherein R_1 represents an aliphatic or cycloaliphatic hydrocarbon radical containing from 3 to 5 carbon atoms.

3. Compounds of the general formula



in which R_2 represents chlorine or bromine and R_5 represents an aliphatic or cycloaliphatic hydrocarbon radical containing 2 to 8, especially 3 to 5, carbon atoms.

4. N - 4 - Chlorobenzenesulphonyl - N¹-*n*-butyl-urea.

5. N - 4 - Chlorobenzenesulphonyl - N¹-cyclohexyl-urea.

6. N - 4 - Bromobenzenesulphonyl - N¹-*n*-butyl-urea.

7. N-(4-Methyl-3-Chlorobenzenesulphonyl)-N¹-(*n*-butyl)-urea.

8. N-(4-Methyl-3-Chlorobenzenesulphonyl)-N¹-isobutyl-urea.

9. Salts of any one of the compounds claimed in any one of claims 1—8, with bases yielding physiologically tolerable salts with such compound.

10. A process for the manufacture of a compound claimed in any one of claims 1—8, conducted substantially as hereinbefore described.

11. A preparation for oral administration and lowering the blood sugar level in the treatment of diabetes mellitus which comprises a compound as claimed in claim 1 in admixture or conjunction with a pharmaceutically suitable carrier.

12. A preparation for oral administration and lowering the blood sugar level in the treatment of diabetes mellitus, which comprises a compound as claimed in any one of claims 2 to 8 in admixture or conjunction with a pharmaceutically suitable carrier.

13. A preparation for oral administration and lowering the blood sugar level in the treatment of diabetes mellitus, which comprises a salt of a compound as claimed in claim 1 with a base yielding a physiologically tolerable salt with such compound in admixture or con-

junction with a pharmaceutically suitable carrier.

14. A preparation for oral administration and lowering the blood sugar level in the treatment of diabetes mellitus, which comprises a salt of a compound as claimed in any one of claims 2 to 8 with a base yielding a physiologically tolerable salt with such compound, in admixture or conjunction with a pharmaceutically suitable carrier.

15. A preparation as claimed in any one of claims 11 to 14 which contains a dosage quantity of 0.5 grams of the sulphonyl-urea compound or salt thereof.

16. A preparation for oral administration and lowering the blood sugar level in the treatment of diabetes mellitus, substantially as described in Example 6 herein.

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MD

ERRATA

SPECIFICATION NO. 808,073

Page 1, line 48, *under* "R_2 in capsule" *insert* "R_3".

Page 3, line 21, *after* "mice" *read* ",".

Page 5, line 16, *after* "and" *read* ",".

THE PATENT OFFICE,
15th July, 1959

DB 11481/1(18)/3807 150 7/59 R

* C L M S *