

PATENT SPECIFICATION

NO DRAWINGS

1.185.090



Date of Application (No. 46808/67) and filing Complete Specification: 13 Oct., 1967.

Application made in Germany (No. F50451 IVb/12o) on 15 Oct., 1966.

Complete Specification Published: 18 March, 1970.

Index at acceptance:—C2 C(1J1A6, 1J1A9, 1J1B, 1J1C2, 1J1Z, 2D43F, 2D43M, 2D43S2, 2D43Z1)

International Classification:—C 07 c 143/78

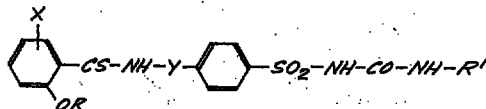
COMPLETE SPECIFICATION

Benzenesulphonyl-Ureas and process for preparing them

We, FARBWERKE HOECHST AKTIENGESELLSCHAFT, Vormalis Meister Lucius & Brüning, a Company recognised by German Law, of, 6230 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:—

The present invention is concerned with new benzene-sulphonyl-ureas and with their manufacture and use.

The present invention provides benzenesulphonyl-ureas of the general formula



and their physiologically tolerable salts. The new benzene-sulphonyl-ureas, in the free form or in the form of their physiologically tolerable salts, have blood sugar lowering properties and are distinguished by a strong hypoglycemic action.

In the above formula

Y represents a $-\text{CH}_2-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-\text{CH}_2-$ or $-\text{CH}_2-\text{CH}(\text{CH}_3)-$ group;

R represents an alkyl radical containing 1 to 5 carbon atoms, preferably a methyl group or a low molecular weight alkenyl, methoxymethyl, ethoxymethyl, methoxyethyl or ethoxyethyl radical;

X represents a halogen atom preferably chlorine; a low molecular weight alkyl radical, preferably a methyl group; a low molecular weight alkoxy radical, preferably a methoxy group, or a trifluoromethyl group;

R¹ represents

(a) an alkyl radical containing 3 to 6 carbon atoms,

(b) a cycloalkyl radical containing 5 to 8 carbon atoms,

(c) a cyclohexenyl or methylcyclohexenyl radical,

(d) a cyclohexyl radical substituted by 1 or 2 alkyl groups, the alkyl groups each containing 1 or 2 carbon atoms and standing preferably in the 4-position of the cyclohexyl radical,

(e) a chlorocyclohexyl radical, or a low molecular weight alkoxy-cyclohexyl radical;

(f) an endomethylene-cyclohexyl, endomethylenecyclohexenyl, endomethylene-cyclohexylmethyl or endomethylene-cyclohexenylmethyl radical;

(g) a norticycyl radical; or

(h) an adamantyl radical.

The substituent represented by X is in the 3- or 4-position or, preferably, in the 5-position to the thiocarbonamide group.

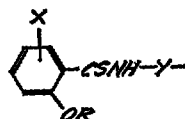
The term "low molecular weight" used throughout the specification is intended to mean groups containing 1 to 4 carbon atoms in a straight or branched chain.

In accordance with the definitions given above, R may represent, for example, methyl, ethyl, propyl, isopropyl, butyl isobutyl or tertiary butyl.

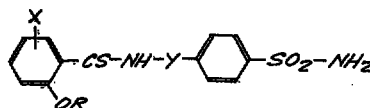
R¹ may represent, for example, a cyclohexyl, 4-methylcyclohexyl (preferably in the trans-form), 4-ethylcyclohexyl, 2,5-endomethylene-cyclohexenyl-methyl, 2,5-endomethylene-cyclohexyl-methyl, butyl, 2,5-endomethylene-cyclohexyl, cycloheptyl, cyclo-octyl or 4,4-dimethylcyclohexyl radical.

The present invention furthermore provides a process for preparing the new benzenesulphonyl-ureas, which comprises

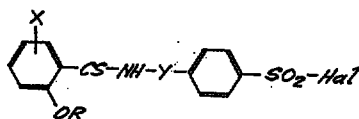
- a) reacting a benzenesulphonyl-isocyanate, benzenesulphonyl-carbamic acid ester, benzenesulphonylthiolcarbamic acid ester, benzenesulphonyl-urea, benzenesulphonyl-semicarbazide or benzenesulphonyl-semicarbazone, which are substituted in *p*-position by the group



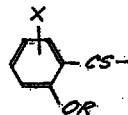
- b) with an R¹-substituted amine or a salt thereof, or reacting a benzenesulphonamide of the formula



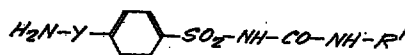
- or a salt thereof with an R¹-substituted isocyanate, carbamic acid ester, thiol-carbamic acid ester, carbamic acid halide or urea, or c) reacting a benzene-sulphohalide of the formula



- d) with an R¹-substituted urea or an alkali metal salt thereof, or hydrolyzing a correspondingly substituted benzenesulphonyl-isourea ether, benzenesulphonyl-isourea ester, benzenesulphonyl-isothiurea ether, benzenesulphonyl-parabanic acid or a benzenesulphonyl-haloformic acid amidine, or e) replacing the sulphur atom in the thiourea radical of a correspondingly substituted benzenesulphonyl-thiourea by an oxygen atom, or f) adding on the elements of water to a correspondingly substituted carbodiimide, or g) hydrogenating a corresponding benzenesulphonyl-urea which contains an unsaturated linkage in the molecule, or h) introducing by acylation the radical



in one or more steps into a benzenesulphonyl-urea of the formula



and, if desired, converting the reaction product so obtained into a salt by treatment with an alkaline agent.

The benzenesulphonyl-carbamic acid ester or benzenesulphonyl-thiolcarbamic acid ester may carry in the alcohol component an alkyl group or an aryl group or even a heterocyclic radical. Since this group is split off during the reaction, its chemical constitution has no influence on the nature of the final product and may, therefore, be varied within wide limits. The same applies to the R¹-substituted carbamic acid esters or to the corresponding thiolcarbamic acid esters.

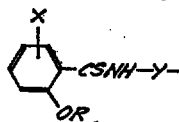
As carbamic acid halides, the chlorides are advantageously used.

The benzenesulphonyl-ureas used as starting materials in the process of the present invention may be unsubstituted at the side of the urea molecule opposite to the sulphonyl group or may be mono- or especially di-substituted. Since these substituents are split off during the reaction with the amine, their nature can be varied within wide limits. In addition to benzenesulphonyl-ureas which carry alkyl-, aryl-, acyl or heterocyclic substituents, there may also be used bis-(benzenesulphonyl)-ureas which may carry at one of the nitrogen atoms a further substituent, for example, a methyl group. Such a bis-(benzenesulphonyl)-urea or also an N-benzenesulphonyl-N'-acyl-urea may be treated with an amine of the formula R^1-NH_2 and the salt so obtained may be heated to an elevated temperature, in particular to a temperature above $100^\circ C$.

Furthermore, it is possible to start from a urea of the formula



or from such a urea which is mono- or especially di-substituted at the free nitrogen atom and to react it with a benzene-sulphonamide carrying the substituent



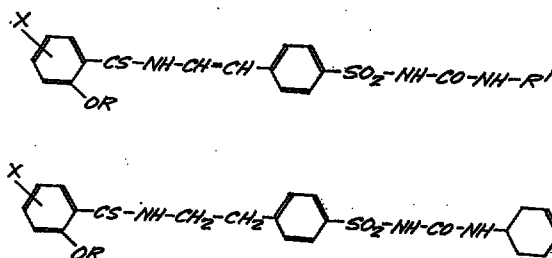
or with a salt thereof. As such starting materials, there may be used, for example, N-cyclohexyl- or N-(4-methyl)-cyclohexyl-urea, the corresponding N'-acetyl-, N'-nitro-, N'-cyclohexyl-, N'-(4-methyl-cyclohexyl)-, N',N'-diphenyl- (in which case the two phenyl radicals may also be substituted or be linked with each other either directly or by means of a bridge member such, for example, as $-CH_2-$, $-NH-$, $-O-$ or $-S-$), N'-methyl-N'-phenyl-, N',N'-dicyclohexyl-ureas as well as R^1 -substituted carbamoyl-imidizoles or triazoles, and finally also ureas of the formula



The hydrolysis of the benzenesulphonyl-parabanic acids, benzenesulphonyl-isourea ethers, benzenesulphonyl-isothioureas, benzenesulphonyl-isourea esters or benzenesulphonyl-haloformic acid amidines mentioned as starting substances is suitably carried out in an alkaline medium. Isourea ethers, isourea esters and haloformic acid amidines may also be hydrolyzed successfully in an acid medium.

The replacement of the sulphur atom in the urea part of correspondingly substituted benzenesulphonyl-thioureas by an oxygen atom can be effected in known manner, for example, with the aid of oxides or salts of heavy metals or with the use of oxidizing agents such, for example, as nitrous acid.

Correspondingly substituted benzenesulphonyl-ureas, which contain an unsaturated linkage in the molecule, for example



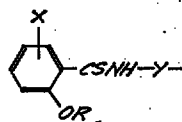
can be converted into the benzenesulphonyl-ureas of the present invention by hydrogenation, for example, with molecular hydrogen, in the presence of a known hydrogenation catalyst.

The acylation of aminoethyl-benzenesulphonyl-ureas may be carried out either in one step, for example by the reaction of a correspondingly substituted thiobenzoic acid halide, or it may be effected in several steps.

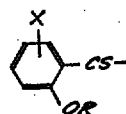
With regard to reaction conditions, the manner of carrying out the process of the present invention may, in general, be varied within wide limits and adapted to each individual case. For example, the reactions may be carried out with the use of solvents or without solvents, at room temperature or at an elevated temperature.

Depending on the nature of the starting substances, one or the other of the processes hereinbefore described may, in some cases, provide a desired, individual benzene-sulphonyl-urea only in small yield or may be inappropriate for its synthesis. In such comparatively rare cases, the expert will have no difficulty in synthesizing the desired product according to another of the processes described.

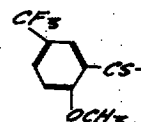
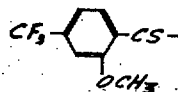
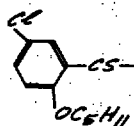
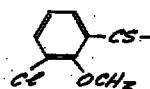
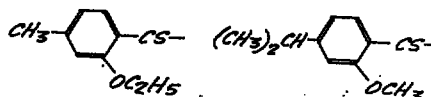
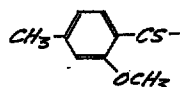
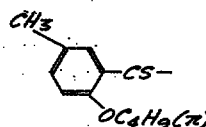
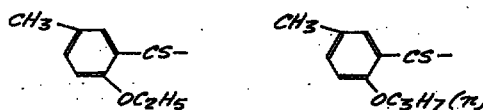
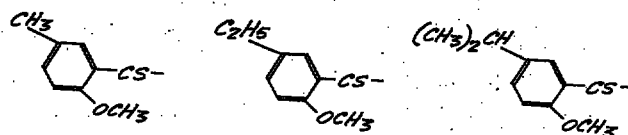
As starting materials, there may be used compounds which contain a benzene radical which is substituted in the *p*-position by the group

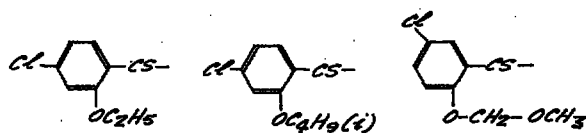
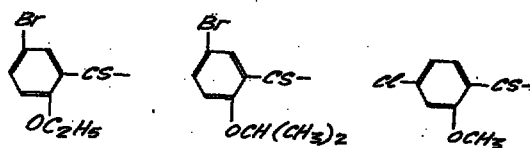
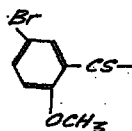
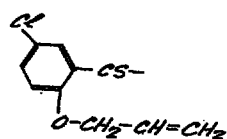
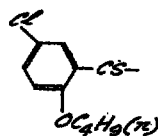
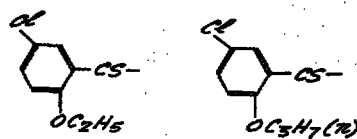
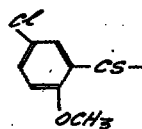
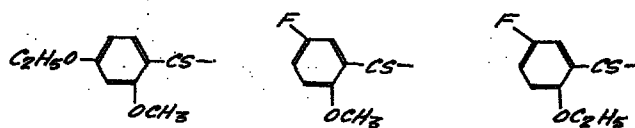
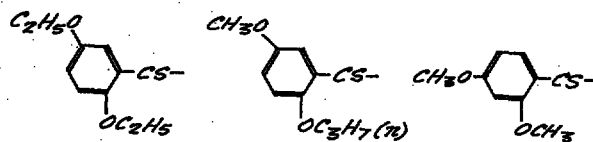
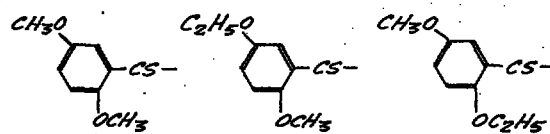


Examples of the component



of the formula indicated above are:





The blood sugar lowering action of the benzenesulphonyl-ureas of the present invention was ascertained by administering them, for example, to rabbits in doses of 10 mg/kg of body weight and determining the blood sugar value according to the known method of Hagedorn-Jensen or by means of an autoanalyser for a prolonged period of time.

Thus, we have found, for example, that 10 mg/kg of body weight of N - [4 - (β - <2 - methoxy - 5 - chloro - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea and 10 mg/kg of body weight of N - [4 - (β - <2 - methoxy - 5 - chloro - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - butyl urea provoke after 3 hours a lowering of the blood sugar of 27 and 25%, respectively, and after 24 hours a lowering of 40 and 38%, respectively.

In the same manner, we have found that 10 mg/kg of body weight of N - [4 - (β - <2 - methoxy - 5 - chloro - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - (4-methyl-cyclohexyl)-urea (trans) provoke after 3 hours a lowering of the blood sugar of 23%, after 24 hours a lowering of 40% and even after 48 hours a lowering of 27%, whereas the known N - (4-methyl - benzene - sulphonyl) - N' - butyl - urea has no blood sugar lowering effect when administered to rabbits in a dose of less than 25 mg/kg of body weight.

The strong hypoglycemic action of the described benzenesulphonyl-ureas becomes more evident when the dose is further reduced. When N - [4 - (β - <2 - methoxy - 5 - chloro - thiobenzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea is administered to a rabbit in a dose of 0.15 mg/kg of body weight or N - [4 - (β - <2 - methoxy - 5 - chloro - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - (4-methylcyclohexyl) - urea (trans) in a dose of 0.05 mg/kg of body weight, a distinct lowering of the blood sugar can still be observed.

The benzenesulphonyl-ureas of the present invention are preferably used for the manufacture of orally administrable pharmaceutical preparations for the lowering of the blood sugar level in the treatment of diabetes mellitus and may be used as such or in the form of their physiologically tolerable salts or in the presence of substances which cause such salt formation. For the formation of salts, there may be used, for example, bases such, for example, as alkali metal or alkaline earth metal hydroxides or alkali metal or alkaline earth metal carbonates or bicarbonates.

The present invention, therefore, also provides a pharmaceutical preparation which comprises a benzenesulphonyl-urea of the above general formula, or a physiologically tolerable salt thereof, in admixture or conjunction with a pharmaceutically suitable carrier.

The pharmaceutical preparations are advantageously in the form of tablets and the pharmaceutically suitable carrier may be, for example, talc, starch, lactose, tragacanth or magnesium stearate.

A pharmaceutical preparation, for example, a tablet or a powder, containing a benzenesulphonyl-urea of the invention or a physiologically tolerable salt thereof as the active substance, with or without one of the aforementioned carriers, is advantageously brought into a suitable unit dosage form. The dose chosen should comply with the activity of the benzenesulphonyl-urea or of the physiologically tolerable salt thereof used and the desired effect. Advantageously, the dosage per unit is within the range of from 0.5 to 100 mg, preferably 2 to 10 mg, but considerably higher or lower dosage units may also be used, which, if desired, are divided or multiplied prior to their administration.

The following Examples illustrate the present invention:—

EXAMPLE 1

N-[4-(β -<2-methoxy-5-chloro-thio-benzamido>-ethyl)-benzenesulphonyl]N'-cyclohexyl-urea

6.5 Grams of 4 - (β - <2 - methoxy - 5 - chloro - thio - benzamido> - ethyl) - benzenesulphonamide (melting point 191—193°C; prepared by the reaction of 2 - methoxy - 5 - chloro - thiobenzoic acid - β - phenylethyl amide with chlorosulphonic acid and ammonia) were dissolved in 8.5 millilitres of a binormal sodium hydroxide solution and 40 millilitres of acetone and to this solution there were added dropwise, at 0—5°C, 2.3 grams of cyclohexyl-isocyanate. The whole was then stirred for 3 hours, diluted with water, filtered and the filtrate was acidified with dilute hydrochloric acid. After recrystallization from methanol, the N - [4 - (β - <2 - methoxy - 5 - chloro - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea obtained was found to melt at 171—172°C.

In analogous manner there were obtained:

- 5 N - [4 - (β - <2 - methoxy - 5 - chloro - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - butyl - urea, melting point 120—122°C (from methanol),
 N - [4 - (β - <2 - methoxy - 5 - chloro - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 153—154°C (from methanol) and
 10 N - [4 - (β - <2 - methoxy - 5 - chloro - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - (4,4 - dimethyl - cyclohexyl) - urea, melting point 166—168°C (from a mixture of methanol and dimethylformamide);
 from
 4 - (β - <2 - methoxy - 5 - methyl - thio - benzamido> - ethyl) - benzenesulphonamide, (melting point 182—184°C):
 15 N - [4 - (β - <2 - methoxy - 5 - methyl - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 170—172°C (from methanol) and
 N - [4 - (β - <2 - methoxy - 5 - methyl - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - (2,4 - dimethyl - cyclohexyl) - urea, melting point 181—183°C (from methanol);
 20 from
 4 - (β - <2 - ethoxy - 5 - chloro - thio - benzamido> - ethyl) - benzenesulphonamide (melting point 126—128°C):
 N - [4 - (β - <2 - ethoxy - 5 - chloro - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclo - hexyl urea, melting point 181—183°C (from a mixture of methanol and dimethylformamide) and
 25 N - [4 - (β - <2 - ethoxy - 5 - chloro - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 178—180°C (from a mixture of methanol and dimethylformamide).

EXAMPLE 2

- 30 N-[4-(β -<2-methoxy-5-bromo-thio-benzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea
 9.7 Grams of N - [4 - (β - <2 - methoxy - 5 - bromo - thio - benzamido> - ethyl) - benzenesulphonyl] - methyl - urethane (prepared by the reaction of 4 - (β - <2 - methoxy - 5 - bromo - thio - benzamido> - ethyl) - benzenesulphonamide (melting point 198—200°C) with chloroformic acid methyl ester) in 100 ml of dioxane were
 35 combined with 2 grams of cyclohexylamine. The whole was heated for 1.5 hours to 110°C, during which time the methanol that had formed distilled off. After cooling, a small amount of water was added and the N - [4 - (β - <2 - methoxy - 5 - bromo - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea that had formed was filtered off with suction and recrystallized from methanol. Melting point 166—167°C.

In analogous manner there were obtained:

- N - [4 - (β - <2 - methoxy - 5 - bromo - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - butyl - urea, melting point 124—126°C (from methanol),
 45 N - [4 - (β - <2 - methoxy - 5 - bromo - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 171—173°C (from methanol),
 N - [4 - (β - <2 - methoxy - 5 - bromo - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - ethyl - cyclohexyl) - urea (trans), melting point 188—189°C (from methanol) and
 50 N - [4 - (β - <2 - methoxy - 5 - bromo - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - (2,4 - dimethyl - cyclohexyl) - urea, melting point 193—194°C (from methanol).

EXAMPLE 3

- 55 N-[4-(β -<2-methoxy-5-chloro-thio-benzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea
 3.85 Grams of 4 - (β - <2 - methoxy - 5 - chloro - thio - benzamido> - ethyl) - benzenesulphonamide were dissolved in 100 millilitres of dimethylformamide and combined, while stirring, with 0.54 gram of sodium methylate (dissolved in 10 millilitres of methanol). The whole was stirred for 10 minutes and then 2.94 grams of N,N - diphenyl - N' - cyclohexyl - urea were added. The mixture was heated for 50 minutes
 60 to 110—115°C, while stirring, during which time the methanol was distilled off over a descending cooler. After cooling, the reaction solution was poured into aqueous ammonia having a strength of about 1%, filtered and the filtrate was acidified. The pre-

precipitate obtained was filtered off with suction, dissolved in aqueous ammonia having a strength of about 1% and precipitated again by acidification. The N - [4 - (β - <2 - methoxy - 5 - chloro - thio - benzamido> - ethyl) - benzene - sulphonyl] - N' - cyclohexyl - urea was found to melt, after recrystallization from dilute methanol, at 171—172°C.

EXAMPLE 4

N - [4 - (β - <2 - methoxy - 5 - chloro - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea

2.15 Grams of N - [4 - (β - <2 - methoxy - 5 - chloro - thio - benzamido> - ethyl) - benzenesulphonyl] - urea (prepared by the reaction of N - (4 - β - <2 - methoxy - 5 - chloro - thio - benzamido> - ethyl) - benzene - sulphonamide with potassium cyanate in aqueous ethanol by boiling under reflux, melting point 168—170°C (from methanol)) were dissolved in 100 millilitres of dioxane and 100 millilitres of xylene. 0.99 Gram of cyclohexylamine was added and the whole was heated for 1 1/2 hours under reflux to the boil. After pouring into water, there was obtained by acidification a precipitate which was filtered off with suction, dissolved in ammonia having a strength of 1% and precipitated again by acidification. The N - [4 - (β - <2 - methoxy - 5 - chloro - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea thus obtained was found to melt after recrystallization from methanol, at 170—172°C.

EXAMPLE 5

N - [4 - (β - <2 - methoxy - 5 - chloro - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea

2.63 Grams of N - [4 - (β - <2 - methoxy - 5 - chloro - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - thiourea (prepared from the corresponding sulphonamide by boiling with cyclohexyl-isothiocyanate in a mixture of dioxane and acetone in the presence of potassium carbonate; melting point 169—171°C) were dissolved in 200 ml of acetone and combined, at a temperature in the range of 0—5°C, while stirring, with sodium nitrite dissolved in a small amount of water. 10 millilitres of 5N-acetic acid were then added dropwise and the whole was stirred for 5 hours at room temperature. The acetone was then removed by distillation under reduced pressure, the residue was combined with water and acidified. The precipitate of N - [4 - (β - <2 - methoxy - 5 - chloro - 5 - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexylurea this obtained was found to melt at 170—172°C, after recrystallization from methanol.

In analogous manner, there were obtained:

from N - [4 - (β - <2 - methoxy - 5 - chloro - thio - benzamido> - ethyl) - benzene - sulphonyl] - N' - cyclooctyl - thio - urea (melting point 177—179°C, from methanol) by treatment with nitrous acid;

N - [4 - (β - <2 - methoxy - 5 - chloro - thio - benzamido> - ethyl) - benzene - sulphonyl] - N' - cyclooctyl - urea, melting at 155°C (after recrystallization from dilute methanol; and from

N - [4 - (β - <2 - methoxy - 5 - chloro - thio - benzamido> - ethyl) - benzene - sulphonyl] - N' - (2,5 - endomethylene - cyclohexyl - methyl) - thio - urea, melting point 176—178°C;

N - [4 - (β - <2 - methoxy - 5 - chloro - thio - benzamido> - ethyl) - benzene - sulphonyl] - N' - (2,5 - endomethylene - cyclohexyl - methyl) - urea, melting point 170—172°C, (from methanol).

EXAMPLE 6

N - [4 - (β - <2 - methoxy - 5 - chloro - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea

2.3 Grams of 4 - (β - <2 - methoxy - 4 - chloro - thio - benzamido> - ethyl) - benzene - sulphonamide (melting point 152—154°C) were dissolved in 50 millilitres of acetone and 50 millilitres of dioxane. 1.7 Grams of potassium carbonate were added and the whole was heated for 1 1/2 hours, while stirring, to 70°C. After addition of 0.75 gram of cyclohexyl-isocyanate, heating at 70°C was continued for 5 hours, while stirring. The whole was then allowed to cool and acidified. The precipitate obtained was taken up in aqueous ammonia having a strength of about 1%. By acidification of the solution, which had been filtered over charcoal, a precipitate of N - [4 - (β - <2 - methoxy - 4 - chloro - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea was obtained which was found to melt at 174—176°C (with decomposition), after recrystallization from dilute methanol.

EXAMPLE 7

N-[4-(β-<2-methoxy-5-chloro-thio-benzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea

16.3 Grams of N - [4 - (β - amino - ethyl) - benzenesulphonyl] - N' - cyclohexyl-urea were suspended in 130 millilitres of chloroform. After addition of 9 grams of pyridine, 11 grams of 2 - methoxy - 5 - chloro - thio - benzoyl chloride, which had been dissolved in 20 millilitres of chloroform, were added dropwise while stirring. The whole was heated for 6 hours, while stirring, to 40—45°C, concentrated under reduced pressure and the residue thus obtained was treated with aqueous ammonia having a strength of about 1%. By acidification of the filtrate with hydrochloric acid, there was obtained N - [4 - (β - <2 - methoxy - 5 - chloro - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea which was found to melt, after 2 recrystallizations from methanol, at 170—172°C.

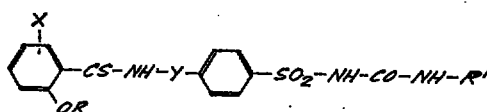
EXAMPLE 8

N-[4-(β-<2-methoxy-5-chloro-thio-benzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea

1.3 Grams of N - [4 - (β - <2 - methoxy - 5 - chloro - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - thiourea (prepared from the corresponding sulphonamide and cyclohexyl-isothiocyanate; melting point 169—171°C, with decomposition) were dissolved in 20 millilitres of dioxane and 50 millilitres of a 1N-sodium hydroxide solution. 0.55 Gram of mercury oxide was added and the whole was stirred for 4 hours at 60°C. After filtration, the diluted solution was acidified with hydrochloric acid, the precipitate obtained was filtered off with suction, dissolved in ammonia having a strength of about 1% and precipitated by means of acid. The precipitate thus obtained of N - [4 - (β - <2 - methoxy - 5 - chloro - thiobenzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea was found to melt, after recrystallization from a mixture of ethyl acetate/petrol ether and dilute methanol, at 170—172°C with decomposition.

WHAT WE CLAIM IS:—

1. Benzenesulphonyl-ureas of the general formula



in which

Y represents a $-\text{CH}_2-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-\text{CH}_2-$ or $-\text{CH}_2-\text{CH}(\text{CH}_3)-$ group;

R represents an alkyl radical containing 1 to 5 carbon atoms, preferably a methyl group; or a low molecular weight alkenyl, methoxymethyl, ethoxymethyl, methoxyethyl or ethoxyethyl radical;

X represents a halogen atom preferably chlorine; a low molecular weight alkyl radical, preferably a methyl group; a low molecular weight alkoxy radical, preferably a methoxy group, or a trifluoromethyl group;

R' represents

(a) an alkyl radical containing 3 to 6 carbon atoms,

(b) a cycloalkyl radical containing 5 to 8 carbon atoms,

(c) a cyclohexenyl or methylcyclohexenyl radical,

(d) a cyclohexyl radical substituted by 1 or 2 alkyl groups, the alkyl groups each containing 1 or 2 carbon atoms and standing preferably in the 4-position of the cyclohexyl radical,

(e) a chlorocyclohexyl radical, or a low molecular weight alkoxy-cyclohexyl radical;

(f) an endomethylene-cyclohexyl, endomethylenecyclohexenyl, endomethylene-cyclohexylmethyl or endomethylene-cyclohexenylmethyl radical;

(g) a nortricycyl radical; or

(h) an adamantyl radical.

2. N - [4 - (β - <2 - methoxy - 5 - chloro - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea.

3. N - [4 - (β - <2 - methoxy - 5 - chloro - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - butyl - urea.

EXAMPLE 7

N-[4-(β-<2-methoxy-5-chloro-thio-benzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea

16.3 Grams of N-[4-(β-amino-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea were suspended in 130 millilitres of chloroform. After addition of 9 grams of pyridine, 11 grams of 2-methoxy-5-chloro-thio-benzoyl chloride, which had been dissolved in 20 millilitres of chloroform, were added dropwise while stirring. The whole was heated for 6 hours, while stirring, to 40—45°C, concentrated under reduced pressure and the residue thus obtained was treated with aqueous ammonia having a strength of about 1%. By acidification of the filtrate with hydrochloric acid, there was obtained N-[4-(β-<2-methoxy-5-chloro-thio-benzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea which was found to melt, after 2 recrystallizations from methanol, at 170—172°C.

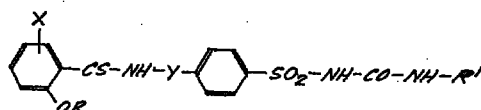
EXAMPLE 8

N-[4-(β-<2-methoxy-5-chloro-thio-benzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea

1.3 Grams of N-[4-(β-<2-methoxy-5-chloro-thio-benzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-thiourea (prepared from the corresponding sulphonamide and cyclohexyl-isothiocyanate; melting point 169—171°C, with decomposition) were dissolved in 20 millilitres of dioxane and 50 millilitres of a 1N-sodium hydroxide solution. 0.55 Gram of mercury oxide was added and the whole was stirred for 4 hours at 60°C. After filtration, the diluted solution was acidified with hydrochloric acid, the precipitate obtained was filtered off with suction, dissolved in ammonia having a strength of about 1% and precipitated by means of acid. The precipitate thus obtained of N-[4-(β-<2-methoxy-5-chloro-thiobenzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea was found to melt, after recrystallization from a mixture of ethyl acetate/petrol ether and dilute methanol, at 170—172°C with decomposition.

WHAT WE CLAIM IS:—

1. Benzenesulphonyl-ureas of the general formula



in which

Y represents a $-\text{CH}_2-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-\text{CH}_2-$ or $-\text{CH}_2-\text{CH}(\text{CH}_3)-$ group;

R represents an alkyl radical containing 1 to 5 carbon atoms, preferably a methyl group; or a low molecular weight alkenyl, methoxymethyl, ethoxymethyl, methoxyethyl or ethoxyethyl radical;

X represents a halogen atom preferably chlorine; a low molecular weight alkyl radical, preferably a methyl group; a low molecular weight alkoxy radical, preferably a methoxy group, or a trifluoromethyl group;

R¹ represents

(a) an alkyl radical containing 3 to 6 carbon atoms,

(b) a cycloalkyl radical containing 5 to 8 carbon atoms,

(c) a cyclohexenyl or methylcyclohexenyl radical,

(d) a cyclohexyl radical substituted by 1 or 2 alkyl groups, the alkyl groups each containing 1 or 2 carbon atoms and standing preferably in the 4-position of the cyclohexyl radical,

(e) a chlorocyclohexyl radical, or a low molecular weight alkoxy-cyclohexyl radical;

(f) an endomethylene-cyclohexyl, endomethylenecyclohexenyl, endomethylene-cyclohexylmethyl or endomethylene-cyclohexenylmethyl radical;

(g) a nortricycyl radical; or

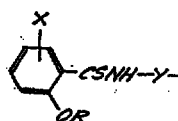
(h) an adamantyl radical.

2. N-[4-(β-<2-methoxy-5-chloro-thio-benzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea.

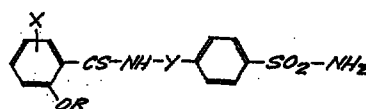
3. N-[4-(β-<2-methoxy-5-chloro-thio-benzamido>-ethyl)-benzenesulphonyl]-N'-butyl-urea.



4. N - [4 - (β - |<2 - methoxy - 5 - chloro - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea.
5. N - [4 - (β - |<2 - methoxy - 5 - chloro - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - (4,4 - dimethyl - cyclohexyl) - urea.
- 5 6. N - [4 - (β - |<2 - methoxy - 5 - methyl - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea.
7. N - [4 - (β - |<2 - methoxy - 5 - methyl - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - (2,4 - dimethylcyclohexyl) - urea.
- 10 8. N - [4 - (β - |<2 - ethoxy - 5 - chloro - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea.
9. N - [4 - (β - |<2 - ethoxy - 5 - chloro - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea.
- 10 10. N - [4 - (β - |<2 - methoxy - 5 - bromo - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea.
- 15 11. N - [4 - (β - |<2 - methoxy - 5 - bromo - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - butyl - urea.
12. N - [4 - (β - |<2 - methoxy - 5 - bromo - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - ethyl - cyclohexyl) - urea.
- 20 13. N - [4 - (β - |<2 - methoxy - 5 - bromo - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - (2,4 - dimethyl - cyclohexyl) - urea.
14. N - [4 - (β - |<2 - methoxy - 5 - bromo - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea.
- 15 15. N - [4 - (β - |<2 - methoxy - 5 - chloro - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclooctyl - urea.
- 25 16. N - [4 - (β - |<2 - methoxy - 5 - chloro - thio - benzamido> - ethyl) - benzenesulphonyl] - N' - (2,5 - endomethylene - cyclohexyl - methyl) - urea.
17. Physiologically tolerable salts of any one of the compounds claimed in claims 1 to 16.
- 30 18. A pharmaceutical 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 1 to 17 in admixture or conjunction with a pharmaceutically suitable carrier.
19. A pharmaceutical preparation as claimed in claim 18, which contains in dosage unit form from 2 to 10 milligrammes of the active ingredient.
- 35 20. A pharmaceutical preparation as claimed in claim 18 or 19, which is in the form of a tablet.
21. A process for the manufacture of benzenesulphonyl-ureas of the general formula given in claim 1 and their salts, which comprises
 - a) reacting a benzenesulphonyl-isocyanate, benzenesulphonyl-carbamic acid ester, benzenesulphonylthiolcarbamic acid ester, benzenesulphonyl-urea, benzenesulphonyl-semicarbazide or benzenesulphonyl-semicarbazone, which are substituted in *p*-position by the group



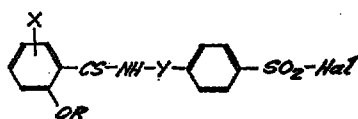
- 45 with an R^1 -substituted amine or a salt thereof, in which R, R^1 , X and Y have the meaning given in claim 1;
- b) reacting a benzenesulphonamide of the formula



- 50 or a salt thereof with an R^1 -substituted isocyanate, carbamic acid ester, thiol-carbamic acid ester, carbamic acid halide or urea, in which R, R^1 , X and Y have the meanings given in claim 1;

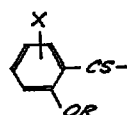


c) reacting a benzene-sulpho-halide of the formula

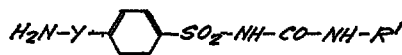


with an R¹-substituted urea or an alkali metal salt thereof, in which R, R¹, X and Y have the meanings given in claim 1;

- 5 d) hydrolyzing a correspondingly substituted benzene-sulphonyl-isourea ether, benzenesulphonyl-isourea ester, benzenesulphonyl-isothiurea ether, benzene-sulphonyl-parabanic acid or a benzenesulphonyl-haloformic acid amidine;
- 10 e) replacing the sulphur atom in the thiourea radical of a correspondingly substituted benzenesulphonyl-thiourea by an oxygen atom;
- f) adding the elements of water to a correspondingly substituted carbodiimide;
- g) hydrogenating a corresponding benzenesulphonyl-urea which contains an unsaturated linkage in the molecule; or
- h) introducing by acylation the radical



15 in which R and X have the meanings given in claim 1, in one or more steps into a benzenesulphonyl-urea of the formula



in which R¹ and Y have the meanings given in claim 1, and, if desired, converting the product so obtained into a salt by treatment with a base.

ABEL & IMRAY,
Chartered Patent Agents,
Quality House, Quality Court,
Chancery Lane, London, W.C.2.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1970.
Published by the Patent Office, 25 Southampton Buildings, London, W.C.2, from which
copies may be obtained.



* C L M S *