

PATENT SPECIFICATION

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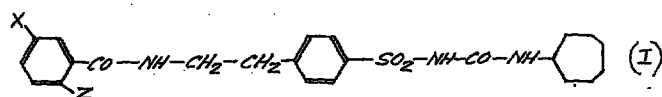
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(54) BENZENESULPHONYL-UREAS AND PROCESS FOR PREPARING THEM

(71) We: FARBWERKE HOECHST AKTIENGESELLSCHAFT, Vormals Meister Lucius & Brüning, of 6230 Frankfurt (M) — 80, P.O. Box 800320, Federal Republic of 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 provides benzenesulphonyl-ureas of the general formula



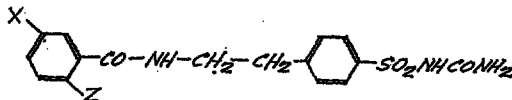
and their physiologically tolerable salts. The benzenesulphonyl-ureas of the above formula are new compounds which, in the free form or in the form of their physiologically tolerable salts, have blood sugar lowering properties and are distinguished by a strong hypoglycemic action.

In the above formula

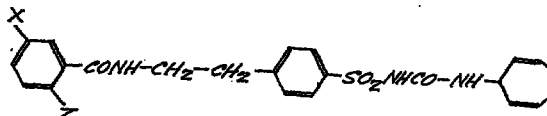
Z represents a hydrogen atom or an alkoxy group containing 1 to 4 carbon atoms, or an allyloxy, methoxymethoxy or ethoxymethoxy group, and

X represents a halogen atom, preferably a chlorine atom, or a methyl, trifluoromethyl or methoxy group or, when Z is an alkoxy or allyloxy group, it may also represent a hydrogen atom.

The present invention furthermore provides a process for preparing the new benzenesulphonyl-ureas, wherein a benzenesulphonyl-urea of the formula

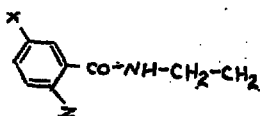


is reacted with a tropylium salt to yield a benzenesulphonylcycloheptatrienyl-urea of the formula

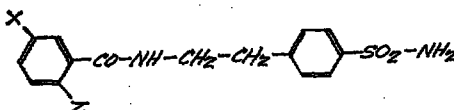


and the cycloheptatrienyl group is catalytically hydrogenated; or

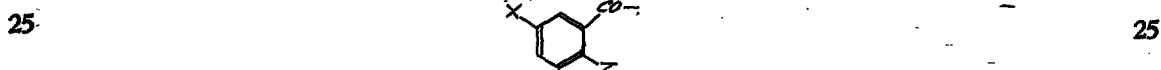
a) a benzenesulphonyl-isocyanate, benzenesulphonyl-carbamic acid ester, benzenesulphonyl-thiolcarbamic acid ester, benzenesulphonyl-carbamic acid halide, benzenesulphonyl-urea, benzenesulphonyl-semicarbazide or a benzenesulphonyl-semicarbazone, which is substituted in *p*-position by the group



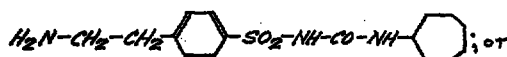
is reacted with cycloheptylamine or a salt thereof; or
b) a benzenesulphonamide of the formula



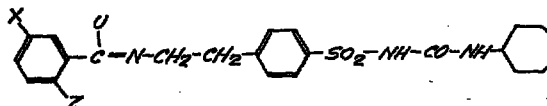
- 5 or a salt thereof is reacted with cycloheptylisocyanate, a cycloheptyl-carbamic acid ester, a cycloheptyl-thiolcarbamic acid ester, a cycloheptyl-carbamic acid halide or a cycloheptyl-urea; or 5
- c) a correspondingly substituted benzenesulphonyl-isourea ether, benzenesulphonyl-isourea ester, benzenesulphonyl-isothiurea ether, benzenesulphonyl-parabanic acid 10
or benzenesulphonyl-haloformic acid amidine is hydrolyzed; or 10
- d) a correspondingly substituted benzenesulphonyl halide is reacted with cycloheptyl-urea, especially with an alkali metal salt thereof; or
- e) a correspondingly substituted benzenesulphinic acid halide, or, in the presence 15
of an acid condensing agent, also a correspondingly substituted benzenesulphinic acid or an alkali metal salt thereof, is reacted with N-cycloheptyl-N'-hydroxy-urea; 15
or
- f) water is added to a correspondingly substituted carbodiimide; or
- g) in a correspondingly substituted benzenesulphonyl-thiourea, the sulphur atom is 20
replaced by an oxygen atom; or
- h) a correspondingly substituted benzenesulphinyl-urea or benzene-sulphenyl-urea 20
is oxidized; or
- i) a corresponding benzenesulphonyl-urea which contains an unsaturated linkage in the molecule is hydrogenated; or
- j) the group



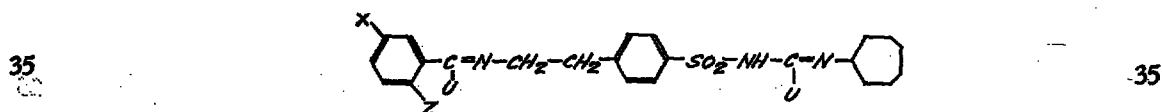
is introduced by acylation in one or more steps into a benzenesulphonyl-urea of the formula



- k) in a correspondingly substituted thio-benzamidoalkylbenzenesulphonyl-urea or 30
thiobenzamidoalkyl-benzenesulphonyl-thiourea, the sulphur atom or the sulphur atoms is or are replaced by an oxygen atom or oxygen atoms; or 30
- l) a compound of the formula



or the parabanic acid derivative thereof or a compound of the formula

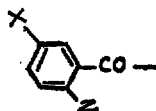


in which each U represents an —O-lower molecular alkyl or —S-lower molecular

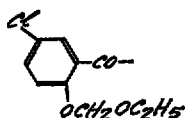
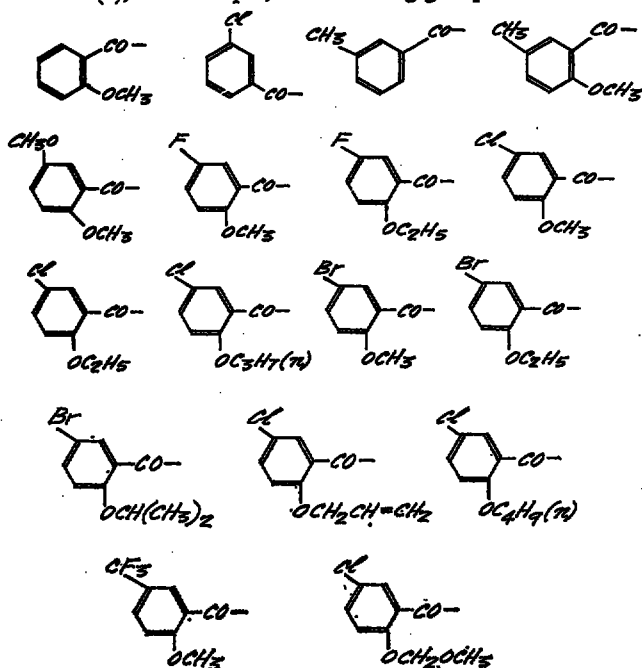
alkyl group or a halogen atom, preferably a chlorine atom is saponified; and, if desired, the reaction product so obtained is converted into a salt by treatment with a base.

The term "lower molecular" used above and hereinafter in connection with organic groups defines those organic groups as containing 1 to 4 carbon atoms.

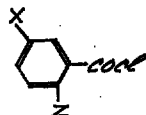
The compounds used as starting substances may contain as the part



of the general formula (I), for example, the following groups:



The starting substances may be prepared according to known methods. Thus, for example, β -phenylethyl-amine may be acylated with an acid chloride of the formula



and the resulting acylamidoethyl-benzene compound may be reacted with chlorosulphonic acid to yield the corresponding acylamidoethyl-benzene-sulphochloride, the latter is converted by means of ammonia into the corresponding acylaminoethyl-benzene-sulphonamide and this is reacted, for example, with potassium cyanate (KOCN) to yield the corresponding acylamidoethyl-benzenesulphonyl-urea.

The reaction of the benzenesulphonyl-ureas with a tropylium salt is suitably carried out in the presence of an acid-binding agent such, for example, as an alkali metal carbonate or bicarbonate. The benzenesulphonyl-ureas used as the starting substances may also be employed in the form of their corresponding salts. As acid-binding agents, there may also be used organic, nitrogen-containing bases, for example, pyridine or triethylamine.

The reaction may suitably be carried out in an aqueous medium; however, aqueous/organic solvents, for example, mixtures of dimethylformamide and water, acetone and water or pure organic solvents such, for example, as pyridine, may also be used.

5 The reaction may be carried out at a temperature of the order of about 20°C. It is also possible to operate at a lower or at a slightly elevated temperature.

The benzenesulphonyl-N'-cycloheptatrienyl-urea derivatives obtained are remarkably pure. If necessary, they can be further purified by recrystallization from alcohols, mixtures of alcohol and water and from other suitable solvents.

10 As tropylium salts, there are preferably used easily water-soluble salts, for example, tropylium bromide.

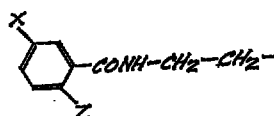
The hydrogenation to yield corresponding benzenesulphonyl-N'-cycloheptyl-urea derivatives is advantageously carried out in alcoholic solution and, in the case of difficultly soluble compounds, in the presence of dimethylformamide. It is, however, also possible to hydrogenate the alkali metal salts of the benzenesulphonyl-N'-cycloheptatrienyl-ureas dissolved in water. As catalysts, there may be used, in general, those which enter into consideration for the hydrogenation of olefinic double linkages, for example, palladium or platinum.

20 The mentioned benzenesulphonyl-carbamic acid esters or benzenesulphonyl-thiol-carbamic acid esters 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 cycloheptyl-substituted carbamic acid esters or to the corresponding thiolcarbamic acid esters.

25 As carbamic acid halides, the chlorides are preferably 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 N-benzenesulphonyl-N'-acyl-urea may be treated with cycloheptyl-amine and the salt obtained may be heated to elevated temperatures, especially to a temperature above 100°C.

35 Furthermore, it is possible to start from cycloheptyl-urea or from a urea which is mono- or especially di-substituted at the free nitrogen atom and to react it with a benzenesulphonamide carrying at the *p*-position, the substituent



40 As such starting materials, there may be used, for example, -N-cycloheptyl-N'-acetyl-, -N'-nitro-, -N'-cycloheptyl-, -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 $-\text{CH}_2-$, $-\text{NH}-$, $-\text{O}-$ or $-\text{S}-$), -N'-methyl-N'-phenyl-, -N', N'-dicyclohexyl-ureas as well as cycloheptyl-substituted cyclohexyl-carbamoyl-imidazoles or -triazoles.

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

50 The reaction of the benzene-sulphonyl-halide with cycloheptyl-urea is suitably carried out using strongly basic condensation agents, for example, an alkali metal, an alkali metal amide or, preferably, an alkali metal hydride, in an inert solvent.

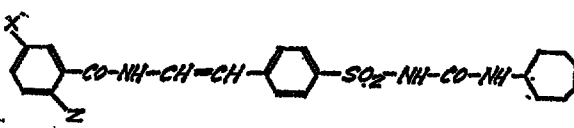
55 The reaction of the sulphinic acid or sulphinic acid chloride with N'-cycloheptyl-N-hydroxy-urea is suitably effected in an inert solvent; however, if a sulphinic acid or an alkali metal salt thereof is used as starting substance, an acid condensation agent, for example, thionyl chloride, polyphosphoric acid, anhydrous phosphoric acid or sulphuric acid, is added.

The replacement of the sulphur atom in a correspondingly substituted benzenesulphonyl-thiourea by an oxygen atom can be effected, for example, with the aid of an oxide or salt of a heavy metal or with the use of an oxidizing agent such, for example, as hydrogen peroxide, sodium peroxide or nitrous acid.

The thioureas may also be desulphurized by treatment with phosgene or with phosphorus pentachloride. The chloroformic acid amidine or chloroformic acid carbodiimide obtained as an intermediate stage may be converted into the benzenesulphonyl-urea by suitable measures, for example, by saponification or addition of water.

The oxidation of the benzenesulphonyl-urea or benzenesulphenyl-urea can be carried out with the aid of a known oxidizing agent, for example, potassium permanganate, in an inert solvent.

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



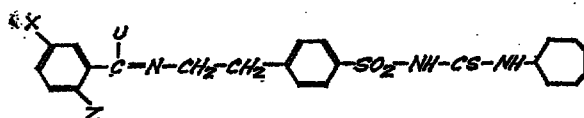
can be converted into the benzenesulphonyl-ureas of the present invention by hydrogenation, for example, with molecular hydrogen, in the presence of a known hydrogenation catalyst.

The acylation of aminoethyl-benzenesulphonyl-ureas may be carried out either in one step, for example, by the reaction of a correspondingly substituted benzoic acid halide, or it may be effected in several steps. As an example of the numerous possibilities of a stepwise acylation, there may be mentioned the reaction of an aminoethyl-benzenesulphonyl-urea with 2-methoxy-benzoyl chloride and the subsequent introduction of a halogen atom into the benzene nucleus of the benzamido group.

The replacement of the sulphur atom in a correspondingly substituted thio-benzamidoalkyl-benzenesulphonyl-urea or -thiourea by an oxygen atom may be effected, for example, with the aid of an oxidizing agent such, for example, as hydrogen peroxide, sodium peroxide or another peroxide compound.

It is also possible to desulphurize, instead of the thiobenzamidoalkyl-benzenesulphonyl-urea, a corresponding thiobenzamidoalkyl-benzenesulphonyl-isothio-urea ether, -isourea ether or ester, -parabanic acid or -haloformic acid amidine, by a treatment with an oxidizing agent in an acid or alkaline medium with simultaneous hydrolytic liberation of the sulphonyl-urea grouping, to yield a benzamidoalkyl-benzenesulphonyl-urea.

In the same way, it is possible to convert, instead of the thio-benzamidoalkyl-benzenesulphonyl-thiourea, a compound of the general formula



in which U has the meaning given above, by a treatment with an oxidizing agent in an acid or alkaline medium with simultaneous desulphuration and hydrolysis, into the corresponding benzamidoalkyl-benzenesulphonyl-urea.

As regards the reaction conditions, the variations a) to l) of carrying out the process of the present invention may, in general, be modified 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 other of the variations of the process hereinbefore described may, in some cases, provide a desired, individual benzenesulphonyl-urea only in a 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 one of the other methods of the process described.

The benzenesulphonyl-N'-cycloheptyl-ureas of the general formula (I) so obtained are distinguished by a strong blood sugar lowering action which was ascertained by administering them, for example, to rabbits, in doses of 10 mg/kg of body weight and determining the blood sugar level 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-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea and 10 mg/kg of body weight of N-[4-(β -{3-chloro-benzamido}-ethyl)-benzenesulphonyl]-N'-(cycloheptyl)-urea provoke after 3 hours a lowering of the blood sugar of 39% and 34%, respectively, and after 24 hours a lowering of 27% and 31%, respectively, whereas the known N-(4-methyl-benzenesulphonyl)-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-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea is administered to a rabbit in a dose of 0.06 mg/kg of body weight or N-[4-(β -{3-chloro-benzamido}-ethyl)-benzenesulphonyl]-N'-(cycloheptyl)-urea in a dose of 0.1 mg/kg of body weight, a distinct lowering of the blood sugar level can still be observed.

The benzenesulphonyl-ureas of the present invention are preferably used for the manufacture of pharmaceutical preparations suitable for oral administration and 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 pharmaceutical preparations which comprise a benzenesulphonyl-urea of the above general formula (I) 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 carriers 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 with the desired effect. Advantageously, the dosage per unit amounts to about 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 invention:—

EXAMPLE 1

(a) N-[4-(β -{3-methyl-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptatrienyl-urea

12 g of N-[4-(β -{3-methyl-benzamido}-ethyl)-benzenesulphonyl]-urea (melting point 200°C) were dissolved in a small excess of 2N-sodium hydroxide solution; the solution was diluted with 150 ml of water and then, 9g of tropylium bromide, dissolved in 50 ml of water, were added slowly and dropwise, at room temperature, while stirring. During this operation, the pH-value of the reaction solution was maintained in the weakly alkaline range by continuous addition of 2N-sodium hydroxide solution. The whole was then stirred for 30 minutes, acidified with dilute acetic acid, whereby the N-[4-(β -{3-methyl-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptatrienyl-urea precipitated. It was found to melt at 141—143°C with decomposition (recrystallized from a mixture of methanol and water).

b) N-[4-(β -{3-methyl-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea

5 g of the compound obtained according to a) were dissolved in methanol with addition of a small amount of dimethylformamide and then hydrogenated with palladium at room temperature. When the absorption of hydrogen was complete, the solvent was removed by evaporation and the residue was recrystallised from aqueous methanol to give the desired product. Melting point 147°C.

In analogous manner, there were obtained from cycloheptatrienyl-ureas which had been prepared in corresponding manner:

N-[4-(β -{2-methoxy-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea, melting point 165°C (from methanol/water); N-[4-(β -{3-chlorobenzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea, melting point 162°C; N-[4-(β -{2-methoxy-5-chlorobenzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea, melting point 140°C (from methanol/water); N-[4-(β -{2-methoxy-5-bromobenzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea, melting point 150°C (from methanol-water; N-

[4 - (β - {2,5 - dimethoxybenzamido} - ethyl) - benzenesulphonyl] - N' - cycloheptyl-urea, melting point 101°C (from methanol/water); N-[4-(β -{2-allyloxy-5-chlorobenzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea, melting point 75°C (methanol/water); and N-[4-(β -{2-ethoxy-5-chlorobenzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea, melting point 140°C (from methanol/water).

EXAMPLE 2

N - [4 - (β - {2 - methoxy - 5 - methyl - benzamido} - ethyl) - benzenesulphonyl] - N'-cycloheptyl-urea

7 g of N-[4-(β -{2-methoxy-5-methyl-benzamido}-ethyl)-benzenesulphonyl]-methyl-urethane (melting point 175—177°C) were suspended in 200 ml of xylene and reacted, at 80°C, with 1.9 g of cycloheptylamine. After a short period of time, the temperature of the oil bath was raised to 150°C and maintained for 30 minutes at this temperature. During this time, the reaction mixture dissolved while the methanol distilled off. Upon cooling, the N-[4-(β -{2-methoxy-5-methyl-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea that had formed precipitated in the form of crystals; after recrystallization from a mixture of methanol and water, the substance was found to melt at 140°C.

EXAMPLE 3

N - [4 - (β - {2 - methoxy - 5 - chloro - benzamido} - ethyl) - benzenesulphonyl] - N'-cycloheptyl-urea

2.45 g of N-[4-(β -{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-phenyl-urethane (obtained from 4-[β -(2-methoxy-5-chloro-benzamido)-ethyl]-benzenesulphonamide and chloroformic acid phenyl ester) were boiled for 2 hours under reflux with 0.5 g of cycloheptylamine in 30 ml of dioxane. After dilution with water and acidification with dilute hydrochloric acid, a precipitate was obtained which was treated with ammonia having a strength of 0.5%. The aqueous alkaline solution was acidified and the precipitate obtained was recrystallized from a mixture of methanol and water. In such a way, N-[4-(β -{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea melting at 140°C was obtained.

EXAMPLE 4

N - [4 - (β - {2 - methoxy - 5 - chloro - benzamido} - ethyl) - benzenesulphonyl] - N'-cycloheptyl-urea

4.26 g of N-[4-(β -{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-methyl-urethane were heated for 1 1/2 hours on a descending cooler with 1.6 g of cycloheptylamine-acetate in 100 ml of dioxane.

After addition of water and recrystallization of the precipitated product from a mixture of methanol and water, there was obtained in a very good yield the N-[4-(β -{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea, melting at 140°C.

EXAMPLE 5

N - [4 - (β - {2 - methoxy - benzamido} - ethyl) - benzenesulphonyl] - N' - cycloheptyl-urea

A mixture of 10 g of N-[4-(β -{2-methoxy-benzamido}-ethyl)-benzenesulphonyl]-urea (melting point 183°C), 300 ml of toluene, 30 ml of glycol monomethyl ether, 1.65 g of glacial acetic acid and 2.8 g of cycloheptylamine was heated for 5 hours under reflux. The whole was then concentrated under reduced pressure and the residue was treated with alcohol. The N-[4-(β -{2-methoxy-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea, obtained as crude product, was filtered off with suction and recrystallized. Melting point 165°C.

EXAMPLE 6

N - [4 - (β - {2 - methoxy - 5 - chloro - benzamido} - ethyl) - benzenesulphonyl] - N'-cycloheptyl-urea

1.06 g of N-[4-(β -{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-N'-methyl-urea (melting point 197—198°C; obtained from N-[4-(β -{2-methoxy-5-chlorobenzamido}-ethyl)-benzenesulphonyl]-methyl urethane and methylamine) and 0.5 g of cycloheptylamine were boiled for 1 1/2 hours under reflux in 30 ml of dioxane. After addition of water and acidification with dilute hydrochloric acid and recrystallization of the product obtained from a mixture of methanol and water, there was obtained in a good yield the N-[4-(β -{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea melting at 140°C.

EXAMPLE 7

N - [4 - (β - {2 - methoxy - 5 - chloro - benzamido} - ethyl) - benzenesulphonyl] - N'-cycloheptyl-urea

5 4.9 g of N-[4-(β -{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-N'-phenyl-urea (melting point 193—195°C), 100 ml of dioxane and 1 g of cycloheptyl-amine were heated for one hour under reflux to the boiling temperature. The clear
10 solution was then concentrated under reduced pressure and the residue obtained was treated with ammonia having a strength of about 0.5%. After clarification of the solution by filtration, the solution was acidified. The precipitate of N-[4-(β -{2-methoxy-5-chloro-benzamido}-ethyl)benzenesulphonyl]-N'-cycloheptyl-urea obtained was filtered
15 off with suction and dried on clay. After recrystallization from a mixture of methanol and water, a pure product melting at 140°C was obtained.

EXAMPLE 8

N - [4 - (β - {2 - methoxy - 5 - chloro - benzamido} - ethyl) - benzenesulphonyl] - N'-cycloheptyl-urea

15 a) 5 g of N-[4-(β -{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-urea were suspended in 30 ml of acetic acid anhydride. 5 Droplets of concentrated sulphuric acid were added and the whole was then heated for 5 minutes on the steam bath. The mixture dissolved and after a short time crystals separated. After the reaction mixture
20 had cooled, the crystals so obtained were filtered off with suction, washed with ethyl acetate and dried. After a short boiling with methanol, the N-[4-(β -{2-methoxy-5-chlorobenzamido}-ethyl)-benzenesulphonyl]-N'-acetyl-urea thus obtained was found to melt at 208°C with decomposition.

25 b) 2.3 g of the product obtained according to a) and 0.5 g of cycloheptylamine were thoroughly mixed. From this operation resulted, with evolution of heat, the cycloheptylamine salt of N-[4-(β -{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-N'-acetyl-urea. The salt was heated for 45 minutes to 150°C in an Erlenmeyer flask on an oil bath. After some minutes, the salt melted while forming a clear
30 molten mass.

The mass was allowed to cool, treated with aqueous ammonia having a strength of 0.5% while heating on a steam bath, filtered and the filtrate was acidified. The crystalline precipitate was filtered off with suction and taken up again in ammonia having a strength of 0.5%.

35 By acidification of the filtrate, there was obtained a crystalline precipitate of N-[4-(β -{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea which was filtered off with suction and dried. After recrystallization from a mixture of methanol and water, the compound was found to melt at 140°C.

EXAMPLE 9

N - [4 - (β - {2 - methoxy - 5 - chloro - benzamido} - ethyl) - benzenesulphonyl] - N'-cycloheptyl-urea

40 2.4 g of N-[4-(β -{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-N,N'-pentamethylene-urea (melting point 181—183°C) and 1 g of cycloheptylamine were boiled for 2 hours under reflux in 35 ml of dioxane. After acidification with dilute hydrochloric acid and recrystallization of the precipitate from a mixture of methanol
45 and water, there was obtained N-[4-(β -{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea in a good yield. The substance was found to melt at 140°C.

EXAMPLE 10

N - [4 - (β - {3 - methyl - benzamido} - ethyl) - benzenesulphonyl] - N' - cycloheptyl-urea

50 6 g of the sodium salt of 4-[β -(3-methyl-benzamido)-ethyl]-benzenesulphonamide were boiled for 3 hours under reflux with 3.9 g of diphenyl carbamic acid chloride in 60 ml of toluene. The crude N-[4-(β -{3-methyl-benzamido}-ethyl)benzenesulphonyl]-N',N'-diphenyl-urea that had formed was filtered off with suction and suspended in
55 dioxane; after addition of 1 g of acetic acid and 1.8 g of cycloheptylamine the whole was boiled for 1 1/2 hours under reflux. After acidification with dilute hydrochloric acid, the precipitate was filtered off with suction and treated with ammonia having a strength of 0.5%. The aqueous alkaline solution was acidified and the crystals were recrystallized from a mixture of methanol and water. There was obtained N-[4-(β -
60 {3-methyl-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea melting at 147°C.

EXAMPLE 11

N - [4 - (β - {2 - methoxy - 5 - chloro - benzamido} - ethyl) - benzenesulphonyl] - N'-cycloheptyl-urea

a) 10 g of the sodium salt of 4-(β-{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonamide and 10.8 g of N-[4-(β-{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-carbamic acid methyl ester were mixed and heated for 30 minutes on an oil bath heated to 175°C. The sintered mass was cooled and treated with aqueous ammonia having a strength of about 0.5%. The resulting solution was filtered and then acidified. The substance that had precipitated was filtered off with suction and taken up again in aqueous ammonia having a strength of 0.5%. After renewed acidification with hydrochloric acid, the resulting precipitate was filtered off with suction and dried on clay. After treatment with ethyl acetate and boiling with ethanol, there was obtained N,N' - bis - [4 - (β - {2 - methoxy - 5 - chloro - benzamido} - ethyl) - benzenesulphonyl]-urea melting at 183—185°C.

b) 0.95 g of the compound obtained according to a) was suspended in 30 ml of dioxane. 0.125 g of cycloheptylamine was added and the whole was heated for 1 hour to the boil under reflux. After concentration of the clear solution obtained, the residue was treated with 0.5% aqueous ammonia, the 4-(β-{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonamide that had formed was filtered off and the filtrate was acidified. There was obtained a crystalline precipitate of N-[4-(β-{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea, which was filtered off with suction, dried and recrystallized from a mixture of methanol and water. The substance was found to melt at 140°C.

EXAMPLE 12

N - [4 - (β - {3 - chloro - benzamido} - ethyl) - benzenesulphonyl] - N' - cycloheptyl-urea

4.75 g of 4-[4-(β-{3-chloro-benzamido}-ethyl)-benzenesulphonyl]-1,1-pentamethylene-semicarbazide (melting point 229°C), 50 ml of dioxane and 1 g of cycloheptylamine were heated for 45 minutes to the boil under reflux. The resulting solution was concentrated under reduced pressure and the residue was taken up in aqueous ammonia having a strength of about 0.5%. The solution was filtered and the filtrate was acidified. A crystalline precipitate of N-[4-(β-{3-chloro-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea was obtained which was filtered off with suction and dried at the air and eventually on the steam bath. After recrystallization from methanol, the substance was found to melt at 162°C.

In analogous manner, there was obtained from 3 g of 4-[4-(β-{3-methyl-benzamido}-ethyl)-benzenesulphonyl]-1,1-pentamethylene-semicarbazide (melting point 241°C) in 50 ml of dimethylformamide and 0.73 g of cycloheptylamine after 1 hour at 120°C in the manner described above, the N-[4-(β-{3-methylbenzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea melting at 147°C (after recrystallization from a mixture of methanol and water).

EXAMPLE 13

N - [4 - (β - {2 - methoxy - 5 - chloro - benzamido} - ethyl) - benzenesulphonyl] - N'-cycloheptyl-urea

A reaction mixture, consisting of 1.8 g of 4-[4-(β-{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-cyclooctanone-semicarbazone (melting point 180—182°C; prepared by heating the sodium salt of 4-(β-{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonamide for 4 hours to 100°C with cyclooctanone-semicarbazone in dimethylformamide), 50 ml of dioxane and 0.33 g of cycloheptylamine, was heated for 1 hour under reflux to the boil. The clear solution was concentrated under reduced pressure and the residue obtained was treated with aqueous ammonia having a strength of about 0.5%. After filtration, the filtrate was acidified. A crystalline precipitate of N - [4 - (β - {2 - methoxy - 5 - chloro - benzamido} - ethyl) - benzenesulphonyl] - N'-cycloheptyl-urea was obtained which was filtered off with suction, dried and recrystallized from methanol. The substance was found to melt at 140°C.

EXAMPLE 14

N - [4 - (β - {2 - methoxy - 5 - methyl - benzamido} - ethyl) - benzenesulphonyl] - N'-cycloheptyl-urea

14 g of 4-(β-{2-methoxy-5-methyl-benzamido}-ethyl)-benzenesulphonamide (melting point 191°C) and 1.7 g of NaOH in 50 ml of H₂O were dissolved in 150 ml

of acetone and the solution was cooled to 0. to 5°C. Then, 4.5 g of cycloheptyl-isocyanate were added dropwise, while stirring, and the whole was stirred for 3 hours at room temperature. The solution was then acidified with dilute hydrochloric acid, the acetone was removed and the substance was reprecipitated from NH₄OH having a strength of 1%. After filtration with suction, there was obtained the N-[4-(β-2-methoxy-5-methyl-benzamido)-ethyl]-benzenesulphonyl]-N'-cycloheptyl-urea which, after recrystallization from a mixture of methanol and water, was found to melt at 166°C.

In analogous manner, there were obtained:

from 4-(β-2-methoxy-5-bromo-benzamido)-ethyl)-benzenesulphonamide (melting point 223—224°C):

N - [4 - (β - { 2 - methoxy - 5 - bromo - benzamido } - ethyl) - benzenesulphonyl]-N'-cycloheptyl-urea, melting point 150°C (recr. from a mixture of methanol and water);

from 4-(β-2,5-dimethoxy-benzamido)-ethyl)-benzenesulphonamide (melting point 169°C):

N - [4 - (β - { 2,5 - dimethoxy - benzamido } - ethyl) - benzenesulphonyl] - N'-cycloheptyl-urea, melting point 101°C (recrystallized from a mixture of methanol and water);

from 4-(β-2-allyloxy-5-chloro-benzamido)-ethyl)-benzenesulphonamide (melting point 183°C):

N - [4 - (β - { 2 - allyloxy - 5 - chloro - benzamido } - ethyl) - benzenesulphonyl]-N'-cycloheptyl-urea, melting point 151°C (recrystallised from a mixture of methanol and water); and

from 4-(β-2-ethoxy-5-chloro-benzamido)-ethyl)-benzenesulphonamide (melting point 174°C):

N - [4 - (β - { 2 - ethoxy - 5 - chloro - benzamido } - ethyl) - benzenesulphonyl]-N'-cycloheptyl-urea, melting point 140°C (recrystallised from a mixture of methanol and water).

EXAMPLE 15

N - [4 - (β - { 2 - methoxy - 5 - chloro - benzamido } - ethyl) - benzenesulphonyl]-N'-cycloheptyl-urea

3.9 g of the sodium salt of 4-(β-2-methoxy-5-chloro-benzamido)-ethyl)-benzenesulphonamide and 4.4 g of N-cycloheptyl-carbamic acid phenyl ester were dissolved in 100 ml of dimethylformamide. The whole was heated for 45 minutes to 110°C, allowed to cool and poured into aqueous ammonia having a strength of about 0.5%. Undissolved matter was filtered off and the filtrate was acidified. The crystalline precipitate that had separated, constituting N-[4-(β-2-methoxy-5-chloro-benzamido)-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea, was filtered off with suction, washed and dried. After recrystallization from methanol, the substance was found to melt at 140°C.

EXAMPLE 16

N - [4 - (β - { 2 - methoxy - 5 - chloro - benzamido } - ethyl) - benzenesulphonyl]-N'-cycloheptyl-urea

3.9 g of the sodium salt of 4-(β-2-methoxy-5-chloro-benzamido)-ethyl)-benzenesulphonamide and 4.26 g of cycloheptyl-urea (melting point 187°C) were thoroughly mixed in a mortar and then heated in an Erlenmeyer flask for 10 minutes on an oil bath heated to 200°C. After cooling, the molten mass was heated on the steam bath with ammonia having a strength of about 0.5%. The whole was filtered and the filtrate was acidified. The precipitate that had separated was filtered off with suction and again taken up in ammonia having a strength of 0.5%. After renewed acidification of the filtrate, the precipitate of N-[4-(β-2-methoxy-5-chloro-benzamido)-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea obtained was filtered off with suction, dried and recrystallized from methanol. The substance was found to melt at 140°C and showed no depression of the melting point with a substance prepared according to another method.

EXAMPLE 17

N - [4 - (β - { 2 - methoxy - 5 - chloro - benzamido } - ethyl) - benzenesulphonyl]-N'-cycloheptyl-urea

3.9 g of the sodium salt of 4-(β-2-methoxy-5-chloro-benzamido)-ethyl)-benzenesulphonamide and 3.7 g of N-acetyl-N'-cycloheptyl-urea were heated for 2 hours to 110°C in 100 ml of dimethylformamide. The solution thus obtained was concentrated under reduced pressure to 2/3 of its volume and then combined with water and hydrochloric acid. The resulting precipitate was filtered off with suction and treated with

aqueous ammonia having a strength of 0.5%. After filtration, the filtrate was acidified and the precipitate of N-[4-(β -{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea thus obtained was filtered off with suction, washed and dried. After recrystallization from a mixture of methanol and water, there was obtained

N-[4-(β -{3-chloro-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea melting at 140°C.

EXAMPLE 18

N-[4-(β -{3-chloro-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea

3.0 g of the sodium salt of 4-(β -{3-chloro-benzamido}-ethyl)-benzenesulphonamide, 5.9 g of N,N-diphenyl-N'-cycloheptyl-urea and 100 ml of dimethylformamide were heated for 45 minutes to 110°C. After some minutes, the whole dissolved to give a clear solution. It was allowed to cool, poured into water and combined with ammonia having a strength of 0.5%. After filtration, the filtrate was acidified. The precipitate obtained was filtered off with suction and introduced again into ammonia having a strength of 0.5%. After filtration and acidification of the filtrate, there was obtained a crystalline precipitate of N-[4-(β -{3-chloro-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea, which was filtered off, washed and dried, first on the air and then in a drying chamber at 60°C. After recrystallization from a mixture of methanol and water, the substance was found to melt at 162°C.

EXAMPLE 19

N-[4-(β -{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea

2 g of the sodium salt of 4-(β -{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonamide and 2.5 g of N,N'-dicycloheptyl-urea (melting point 223°C) were thoroughly mixed in a mortar. The mixture was then heated for 10 minutes to 220°C in an Erlenmeyer flask on a preheated oil bath. After cooling, the sintered reaction cake was treated with ammonia having a strength of 0.5%. After filtration, the filtrate was acidified. There was obtained a precipitate which was filtered off with suction and again taken up in ammonia having a strength of 0.5%. After filtration, the filtrate was acidified. The precipitate that separated and constituted crude N-[4-(β -{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea, was filtered off with suction and dried in the air. By treatment with methanol, there was obtained a substance which at first was smeary but crystallized later and which, after having been filtered off with suction, was again recrystallized from a mixture of methanol and water. The N-[4-(β -{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea thus obtained was found to melt at 140°C.

EXAMPLE 20

N-[4-(β -{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea

a) Potassium salt of N-[4-(β -{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-imino-dithiocarbonic acid

74 g of 4-(β -{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonamide were dissolved in 350 ml of dimethylformamide. 23 g of carbon disulphide and then a solution of 34 g of potassium hydroxide in 50 ml of water were added dropwise, while stirring. The whole was stirred for 3 hours at room temperature and the clear solution was poured into 4 litres of ethanol. The potassium salt of N-[4-(β -{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-imino-dithiocarbonic acid that had precipitated was filtered off with suction, washed with alcohol and dried. Yield: 60 g.

b) N-[4-(β -{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-imino-dithiocarbonic acid dimethyl ester.

36 g of the potassium salt obtained according to a) were dissolved in 60 ml of an 1N-sodium hydroxide solution. To the clear solution, there were added, while shaking, 12.6 g of dimethyl sulphate. The solution became warm. After standing for 30 minutes, the solution was decanted to separate a semi-solid smeary mass that had precipitated. After washing with water, the smeary mass crystallized. The crystals were recrystallized from dilute methanol; in this way, 30 g of N-[4-(β -{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-imino-dithiocarbonic acid dimethyl ester melting at 94-96°C were obtained.

c) N-[4-(β -{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-isothioureia methyl ether.

4.73 g of the ester obtained according to b) were dissolved in 100 ml of dioxane.

1 g of cycloheptylamine was added and the whole was heated for 1½ hours on the steam bath. After pouring into water and acidification with hydrochloric acid, there was obtained the above-specified isothiurea methyl ether in the form of a smeary mass.

d) N - [4 - (β - { 2 - methoxy - 5 - chloro - benzamido } - ethyl) - benzenesulphonyl] - N'-cycloheptyl-urea.

The smeary mass obtained according to c) was dissolved in dioxane, the solution was combined with a 2N-sodium hydroxide solution and heated for 1 hour on the steam bath. After pouring into water and acidification with acetic acid, there was obtained the N-[4-(β-{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea in the form of a crystalline precipitate. After recrystallization from a mixture of methanol and water, the substance was found to melt at 140°C.

EXAMPLE 21

N - [4 - (β - { 2 - methoxy - 5 - chloro - benzamido } - ethyl) - benzenesulphonyl] - N'-cycloheptyl-urea

a) 4.9 g of 1-cycloheptyl-parabanic acid (melting point 172°C) and 2.5 g of triethylamine were dissolved in 200 ml of benzene and combined with 8.9 g of 4-(β-{2-methoxy-5-chloro-benzamido}-ethyl)-benzene-sulphochloride (melting point 102—103°C). The mixture was heated for 3 hours under reflux and the triethylamine hydrochloride that had formed was filtered off with suction, while hot. The cooled filtrate was combined with petroleum ether and the crystals which precipitated after a short period of time were filtered off with suction. After two recrystallizations from mixtures of methanol and dimethylformamide, there was obtained pure 1-[4-(β-{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-3-cycloheptyl-parabanic acid melting at 126°C.

b) 0.5 g of the substance obtained according to a) was heated for 45 minutes on the steam bath with 5 ml of dioxane and 10 ml of 1N-sodium hydroxide solution. The whole was then combined with water, acidified and the precipitate that had separated was recrystallized from methanol. The N-[4-(β-{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea thus obtained was found to melt at 140°C.

EXAMPLE 22

N - [4 - (β - { 2 - methoxy - 5 - chloro - benzamido } - ethyl) - benzenesulphonyl] - N'-cycloheptyl-urea

a) 3 g of N-[4-(β-{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-thiourea (melting point 147°C; prepared by the reaction of 4-(β-{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonamide with cycloheptyl-isothiocyanate in boiling acetone in the presence of potassium carbonate) were suspended in 50 ml of binormal sodium hydroxide solution. Then, 10 ml of hydrogen peroxide having a strength of 35% were added. The whole was heated for 30 minutes on the steam bath, acidified with dilute hydrochloric acid, the crystalline precipitate thus obtained was filtered off with suction and recrystallized from methanol. After recrystallization from a mixture of methanol and water, the isolated N-[4-(β-{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea was found to melt at 140°C.

The same compound was obtained when desulphurizing the thiourea mentioned at the beginning by a treatment with mercury oxide in the presence of a sodium hydroxide solution. For this purpose, 0.5 g of the thiourea was dissolved in 10 ml of dioxane and 10 ml of a binormal sodium hydroxide solution. 0.22 g of HgO was added and the whole was stirred for 4 hours at 40°C. The mercury sulphide that had formed was removed by filtration with suction, the filtrate was acidified and the precipitate of N-[4-(β-{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea that had separated was filtered off with suction and recrystallized from methanol. It was found to melt at 140°C.

b) 0.52 g of N-[4-(β-{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-thiourea were dissolved in 50 ml of methanol. 0.22 g of mercury oxide and a small amount of K₂CO₃ was added, while stirring, and the whole was heated for 3 hours to 50—55°C, while further stirring. After separation by filtration of the mercury sulphide that had formed, the filtrate was concentrated, whereby N-[4-(β-{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-isourea methyl ether melting at 122°C (from ethyl acetate) was obtained. Concentrated hydrochloric acid was poured over a sample of the above-specified isourea ether in a test tube and the whole was heated, while stirring, for some minutes on the steam bath. The crystalline product obtained, constituting N-[4-(β-{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea, was recrystallized from methanol and was then found to melt at 140°C.

EXAMPLE 23

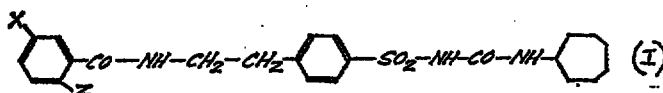
N - [4 - (β - {2 - methoxy - 5 - chloro - benzamido} - ethyl) - benzenesulphonyl]-N'-cycloheptyl-urea

5 g of N-[4-(β -{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-cycloheptyl-thiourea (melting point 147°C) were dissolved in 400 ml of absolute tetrahydrofuran, whereupon dry phosgene was introduced, while stirring. During this operation, the temperature rose to 25—33°C. After having blown through nitrogen to remove any excess of phosgene from the solution, the solution was concentrated under reduced pressure at room temperature. A tough resin was obtained as residue.

An excess quantity of a 2N-sodium hydroxide solution was poured over 2 g of this resin and the whole was heated on the steam bath, while stirring and while adding dioxane as solubilizer. After separation of undissolved matter by filtration, the filtrate was acidified and the N-[4-(β -{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea that had precipitated was filtered off with suction. It was dissolved again in ammonia having a strength of 0.5% and then N-[4-(β -{2-methoxy-5-chloro-benzamido}-ethyl)-benzenesulphonyl]-N'-cycloheptyl-urea was precipitated again, filtered off, dried and recrystallized from a mixture of methanol and water. It was found to melt at 140°C.

WHAT WE CLAIM IS:—

1. Benzenesulphonyl-ureas of the general formula



in which

Z represents a hydrogen atom or an alkoxy group containing 1 to 4 carbon atoms, or an allyloxy, methoxymethoxy or ethoxymethoxy group; and

X represents a halogen atom, or a methyl, trifluoromethyl or methoxy group or, if Z is an alkoxy or allyloxy group, may also represent a hydrogen atom.

2. N - [4 - (β - {2 - methoxy - 5 - methyl - benzamido} - ethyl) - benzenesulphonyl]-N'-cycloheptyl-urea.

3. N - [4 - (β - {2 - methoxy - 5 - chloro - benzamido} - ethyl) - benzenesulphonyl]-N'-cycloheptyl-urea.

4. N - [4 - (β - {2,5 - dimethoxy - benzamido} - ethyl) - benzenesulphonyl]-N'-cycloheptyl-urea.

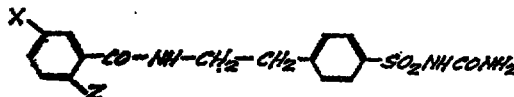
5. N - [4 - (β - {3 - methyl - benzamido} - ethyl) - benzenesulphonyl] - N'-cycloheptyl-urea.

6. N - [4 - (β - {2 - methoxy - benzamido} - ethyl) - benzenesulphonyl] - N'-cycloheptyl-urea.

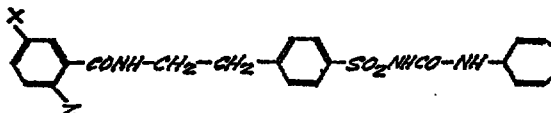
7. Any one of the benzenesulphonyl-ureas as claimed in claim 1, which is specifically mentioned in the Examples herein, other than the compounds claimed in claims 2 to 6.

8. Physiologically tolerable salts of any one of the compounds claimed in any one of claims 1 to 7.

9. A process for the manufacture of benzenesulphonyl-ureas of the general formula (I) given in claim 1, wherein a benzenesulphonyl-urea of the formula



in which X and Z have the meanings given in claim 1, is reacted with a tropylium salt to yield a benzenesulphonyl-cycloheptatrienyl-urea of the formula



and the cycloheptatrienyl group is catalytically hydrogenated; or

a) A benzenesulphonyl-isocyanate, benzenesulphonyl-carbamic acid ester, benzenesulphonyl-thiolcarbamic acid ester, benzenesulphonyl-carbamic acid halide, benzenesulphonyl-urea, benzenesulphonyl-semicarbazide or a benzenesulphonyl-semicarbazone, which is substituted in *p*-position by the group

EXAMPLE 23

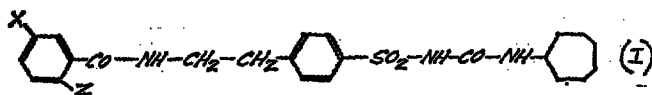
N - [4 - (β - {2 - methoxy - 5 - chloro - benzamido} - ethyl) - benzenesulphonyl] - N'-cycloheptyl-urea

5 g of N - [4 - (β - {2 - methoxy - 5 - chloro - benzamido} - ethyl) - benzenesulphonyl] - cycloheptyl-thiourea (melting point 147°C) were dissolved in 400 ml of absolute tetrahydrofuran, whereupon dry phosgene was introduced, while stirring. During this operation, the temperature rose to 25—33°C. After having blown through nitrogen to remove any excess of phosgene from the solution, the solution was concentrated under reduced pressure at room temperature. A tough resin was obtained as residue.

An excess quantity of a 2N-sodium hydroxide solution was poured over 2 g of this resin and the whole was heated on the steam bath, while stirring and while adding dioxane as solubilizer. After separation of undissolved matter by filtration, the filtrate was acidified and the N - [4 - (β - {2 - methoxy - 5 - chloro - benzamido} - ethyl) - benzenesulphonyl] - N'-cycloheptyl-urea that had precipitated was filtered off with suction. It was dissolved again in ammonia having a strength of 0.5% and then N - [4 - (β - {2 - methoxy - 5 - chloro - benzamido} - ethyl) - benzenesulphonyl] - N'-cycloheptyl-urea was precipitated again, filtered off, dried and recrystallized from a mixture of methanol and water. It was found to melt at 140°C.

WHAT WE CLAIM IS:—

1. Benzenesulphonyl-ureas of the general formula



in which

Z represents a hydrogen atom or an alkoxy group containing 1 to 4 carbon atoms, or an allyloxy, methoxymethoxy or ethoxymethoxy group; and

X represents a halogen atom, or a methyl, trifluoromethyl or methoxy group or, if Z is an alkoxy or allyloxy group, may also represent a hydrogen atom.

2. N - [4 - (β - {2 - methoxy - 5 - methyl - benzamido} - ethyl) - benzenesulphonyl] - N'-cycloheptyl-urea.

3. N - [4 - (β - {2 - methoxy - 5 - chloro - benzamido} - ethyl) - benzenesulphonyl] - N'-cycloheptyl-urea.

4. N - [4 - (β - {2,5 - dimethoxy - benzamido} - ethyl) - benzenesulphonyl] - N'-cycloheptyl-urea.

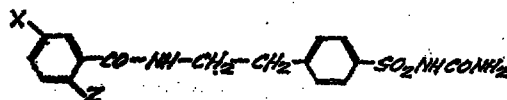
5. N - [4 - (β - {3 - methyl - benzamido} - ethyl) - benzenesulphonyl] - N'-cycloheptyl-urea.

6. N - [4 - (β - {2 - methoxy - benzamido} - ethyl) - benzenesulphonyl] - N'-cycloheptyl-urea.

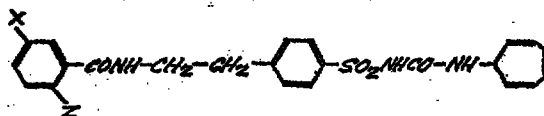
7. Any one of the benzenesulphonyl-ureas as claimed in claim 1, which is specifically mentioned in the Examples herein, other than the compounds claimed in claims 2 to 6.

8. Physiologically tolerable salts of any one of the compounds claimed in any one of claims 1 to 7.

9. A process for the manufacture of benzenesulphonyl-ureas of the general formula (I) given in claim 1, wherein a benzenesulphonyl-urea of the formula



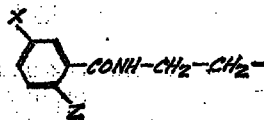
in which X and Z have the meanings given in claim 1, is reacted with a tropylium salt to yield a benzenesulphonyl-cycloheptatrienyl-urea of the formula



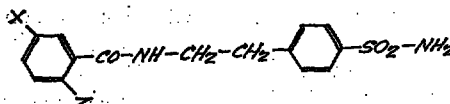
and the cycloheptatrienyl group is catalytically hydrogenated; or

a) A benzenesulphonyl-isocyanate, benzenesulphonyl-carbamic acid ester, benzenesulphonyl-thiocarbamic acid ester, benzenesulphonyl-carbamic acid halide, benzenesulphonyl-urea, benzenesulphonyl-semicarbazide or a benzenesulphonyl-semicarbazone, which is substituted in p-position by the group

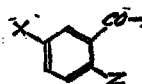




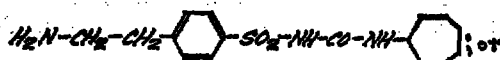
is reacted with cycloheptylamine or a salt thereof; or
b) A benzenesulphonamide of the formula



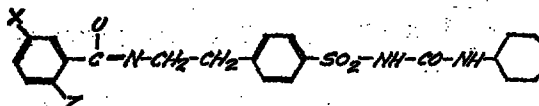
- 5 or a salt thereof is reacted with cycloheptyl-isocyanate, a cycloheptyl-carbamic acid ester, a cycloheptyl-thiocarbamic acid ester, a cycloheptyl-carbamic acid halide or a cycloheptyl-urea; or
c) A correspondingly substituted benzenesulphonyl-isourea ether, benzenesulphonyl-isourea ester, benzenesulphonyl-isothiurea ether, benzenesulphonyl-parabanic acid or a
10 benzenesulphonyl-haloformic acid amidine is hydrolyzed; or
d) A correspondingly substituted benzenesulphonyl halide is reacted with cycloheptyl-urea or an alkali metal salt thereof; or
e) A correspondingly substituted benzenesulphinic acid halide, or, in the presence of
15 an acid condensing agent, also a correspondingly substituted benzenesulphinic acid or an alkali metal salt thereof, is reacted with N-cycloheptyl-N'-hydroxy-urea; or
f) Water is added to a correspondingly substituted carbodiimide; or
g) In a correspondingly substituted benzenesulphonyl-thiourea, the sulphur atom is replaced by an oxygen atom; or
h) A correspondingly substituted benzenesulphenyl-urea or benzene-sulphenyl-urea is
20 oxidized; or
i) A corresponding benzenesulphonyl-urea which contains an unsaturated linkage in the molecule is hydrogenated; or
j) the group



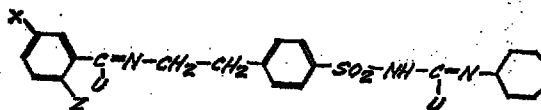
- 25 is introduced by acylation in one or more steps into a benzenesulphonyl-urea of the formula



- k) In a correspondingly substituted thio-benzamidoalkyl-benzenesulphonyl-urea or thiobenzamidoalkyl-benzenesulphonyl-thiourea, the sulphur atom or the sulphur atoms
30 is or are replaced by an oxygen atom or oxygen atoms; or
l) A compound of the formula



or a parabanic acid derivative thereof or a compound of the formula



- 35 in which each U represents an -O-lower molecular alkyl or -S-lower molecular alkyl group or a halogen atom, is saponified; and if desired, the reaction product so obtained is converted into a salt by treatment with a base.

10. 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 8, in admixture or conjunction with a pharmaceutically suitable carrier.

5 11. A pharmaceutical preparation as claimed in claim 10, which contains in dosage unit form from 2 to 10 milligrammes of the active ingredient. 5

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