

PATENT SPECIFICATION

(11) 1203 425

NO DRAWINGS

(21) Application No. 54301/67 (22) Filed 29 Nov. 1967

(31) Convention Application No. F 50793 IVb/12o

(32) Filed 29 Nov. 1966 in

(33) Germany (DT)

(31) Convention Application No. F 52939 IVb/12o

(32) Filed 13 July 1967 in

(33) Germany (DT)

(45) Complete Specification published 26 Aug. 1970

(51) International Classification C 07 c 143/78

(52) Index at acceptance

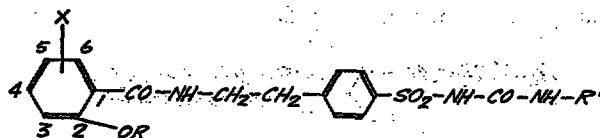
C2C 182—197—280 184—194—279 1Q11G 1Q11J 1Q5
 1Q6B2 1Q8A 1Q9A 1K9F1 1Q9H 215 220 225 227
 22Y 250 252 25Y 30X 30Y 313 314 31Y 338 342
 34Y 351 352 364 36Y 385 396 510 514 525 528 52X
 603 613 615 62X 662 699 790 79Y RIE SB SU



(54) BENZENESULPHONYL UREAS AND PROCESS FOR THEIR MANUFACTURE

(71) We, FARBWERKE HOECHST AKTIENGESELLSCHAFT, Vormalis Meister Lucius & Brüning, of 6230 Frankfurt (M)—80, P.O. Box 800320, Federal Republic of Germany, a Company recognised by German law, 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 benzenesulphonylureas corresponding to the general formula



in which

R represents a lower alkyl radical, preferably methyl, or lower alkenyl radical,
 X represents a hydrogen, fluorine, chlorine or bromine atom, preferably chlorine or a lower alkyl radical, preferably a methyl radical, or a lower alkoxy radical, preferably a methoxy radical,

R¹ represents an endomethylene-cyclohexyl, endomethylene-cyclohexenyl, endoethylene-cyclohexyl, or endoethylene-cyclohexenyl radical.

The substituent X is in the 4- or preferably in the 5-position relative to the carbonyl group.

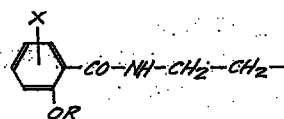
In the above and the following definitions "lower alkyl, alkenyl or alkoxy" always stands for an alkyl, alkenyl or alkoxy group containing 1 to 4 carbon atoms in a straight or branched chain.

According to the above-mentioned definitions R may represent, for example, a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl or allyl group.

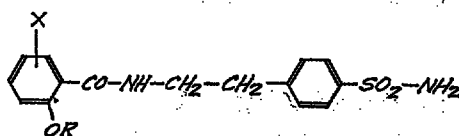
In particular, R¹ may represent a 2,5-endomethylene-cyclohexenyl, 2,5-endomethylenecyclohexyl, 2,5-endoethylenecyclohexyl or a 2,5-endoethylenecyclohexenyl radical.

The present invention also provides a process for the preparation of the benzenesulphonyl-ureas of the above general formula, wherein

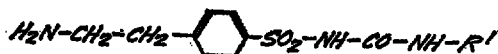
a) a benzenesulphonyl-isocyanate, benzenesulphonyl-carbamic acid ester, benzenesulphonyl-thiocarbamic acid ester, benzenesulphonyl-carbamic acid halide or benzenesulphonyl-urea, benzenesulphonyl-semicarbazide or benzenesulphonyl-semicarbazone substituted in *p*-position by the group



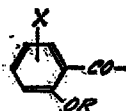
- b) is reacted with an amine, $R'-NH_2$, or, if desired, a salt thereof;
a benzenesulphonamide of the formula



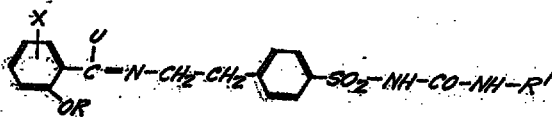
- 5 or a salt thereof is reacted with an R^1 -isocyanate, an R^1 -substituted carbamic acid ester, -thiocarbamic acid ester, carbamic acid halide or -urea;
c) a correspondingly substituted benzenesulphonyl-isourea ether, benzene-sulphonyl-isourea ester, benzenesulphonyl-isothiurea ether, benzenesulphonyl-parabanic acid
10 d) a correspondingly substituted benzenesulphonyl-haloformic acid amidine is hydrolyzed;
e) a correspondingly substituted benzenesulphinic acid halide or, in the presence of an acid condensing agent even a correspondingly substituted benzene-sulphinic acid or an alkali metal salt thereof, is reacted with a hydroxy urea the NH_2
15 group of which being substituted by R^1 ;
f) water is added to a correspondingly substituted carbodiimide;
g) in a correspondingly substituted benzenesulphonyl-thiourea the sulphur atom is exchanged for an oxygen atom;
h) a correspondingly substituted benzenesulphinyl-urea or benzenesulphenyl-urea is
20 oxidized;
i) a corresponding benzenesulphonyl-urea containing in the molecule an unsaturated linkage is hydrogenated,
j) in a benzenesulphonyl-urea of the formula



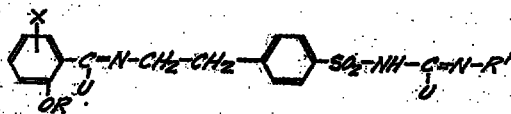
- 25 the radical



- is introduced by acylation, if desired in several stages;
k) in a correspondingly substituted thiobenzamidoethyl-benzene-sulphonyl-urea or
30 -benzenesulphonyl-thiourea the sulphur atom or the sulphur atoms are exchanged for 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



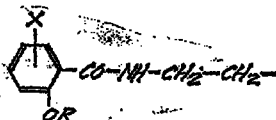
- 35 wherein U represents O-lower alkyl, S-lower alkyl or a halogen atom (preferably chlorine) is saponified,
and, if a salt is desired, the reaction product is treated with a base.

The above-mentioned benzenesulphonyl-carbamic acid esters or the benzenesulphonyl-thiocarbamic acid esters may contain in the alcohol component an alkyl radical or an aryl radical or a heterocyclic radical. Since this radical is split off during the reaction, its chemical constitution has no influence on the character of the final product and can therefore vary within wide limits. The same applies to the R^1 -substituted carbamic acid esters or the corresponding thiocarbamic acid esters.

As carbamic acid halides there are suitable, above all, the chlorides.

The benzenesulphonyl-ureas used as starting substances for the process of the invention may be unsubstituted at the side of the urea molecule opposite to the sulphonyl group or may be mono- or preferably di-substituted. Since these substituents are split off during the reaction with amines, their nature can vary within wide limits. Instead of benzenesulphonyl-ureas substituted by an alkyl, aryl, acyl or heterocyclic radical, there can likewise be used the Bis-(benzenesulphonyl)-ureas, which may carry a further substituent at one nitrogen atom, for example, a methyl group. It is, for example, possible to treat such a bis-(benzenesulphonyl)-urea or N-benzene-sulphonyl-N'-acyl-urea with an amine of the formula R^1NH_2 and to heat the salt so obtained to an elevated temperature, especially to a temperature above $100^\circ C$.

Furthermore, it is possible to start from an urea of the formula $R^1-NH-CO-NH_2$ or from a related urea being mono- or, in particular di-substituted at the free nitrogen atom and to react either of these with a benzenesulphonamide substituted by the grouping



As such starting substances there may be used, for example, N-endomethylenecyclohexyl, or N-endomethylenecyclohexenyl-urea, the corresponding N'-acetyl- or N'-nitro-ureas, N'-endomethylenecyclohexyl-ureas, N'-endomethylenecyclohexenyl-ureas, N',N'-diphenyl-ureas (in which case the two phenyl radicals may be substituted and may be linked with one another directly or by means of a bridge member such, for example, as $-CH_2-$, $-NH-$, $-O-$ or $-S-$), N'-methyl-N'-phenyl- or N',N'-dicyclohexyl-ureas as well as R^1 -substituted cyclohexyl carbamoyl-imidazoles or triazoles.

Hydrolysis of the mentioned benzenesulphonyl-parabanic acids, benzenesulphonyl-isourea-ethers, benzenesulphonyl-isothiourae-ethers, benzenesulphonyl-isourea-esters or benzenesulphonyl-haloformic acid amidines is suitably carried out in an alkaline medium. Isourea-ethers and isourea-esters can be hydrolysed successfully in an acid medium, too.

The reaction of the benzenesulphonyl halides with R^1 -substituted ureas is suitably carried out by using basic condensing agents such, for example, as alkali metals, alkali metal amides or, preferably, alkali metal hydrides in inert solvents.

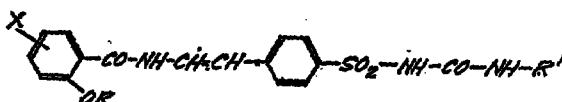
The reaction of the sulphinic acids or sulphinic acid chlorides with hydroxy-ureas can suitably be carried out in inert solvents. If the sulphinic acids or their alkali metals are used as starting substances, acid condensing agents such, for example, as thionyl chloride, polyphosphoric acids, anhydrous phosphoric acid or sulphuric acid are added.

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

Thioureas may also be desulphurized by treating them with phosphorus pentachloride. Chloroformic acid amidines or carbodiimides obtained as intermediate products can be converted into the benzenesulphonyl-ureas by suitable processes such, for example, as saponification or addition of water.

The oxidation of the benzene-sulphinyl- or -sulphenyl-ureas can be carried out

A correspondingly substituted benzenesulphonyl-urea, containing in the molecule with oxidizing agents such, for example, as potassium permanganate in an inert solvent, an unsaturated bond, for example



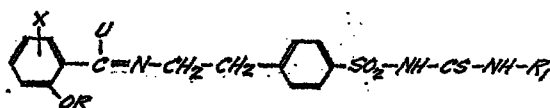
can be converted by hydrogenation, for example, with molecular hydrogen in the presence of a known hydrogenation catalyst to a benzenesulphonyl-urea of the present invention.

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

The sulphur atom in a correspondingly substituted thiobenzamido-ethyl-benzenesulphonyl-urea or thiobenzamidoethyl-benzenesulphonyl-thiourea can be replaced by an oxygen atom, for example, with the aid of an oxidizing agent such, for example, as hydrogen peroxide, sodium peroxide or other peroxide compound.

Instead of the thiobenzamido-ethyl-benzenesulphonyl-urea a corresponding thiobenzamidoethyl-benzenesulphonyl-isothiurea-ether, isourea-ether or -ester, -parabanic acid or thiobenzamidoethyl-benzenesulphonyl-haloformic acid amidine can be desulphurized by treatment with oxidizing agents in an acid or alkaline medium whereby simultaneously a desulphurization and a hydrolysis, to form the sulphonyl-urea grouping, occur and the benzamidoethyl-benzene-sulphonyl-urea is obtained.

Instead of the thiobenzamido-ethyl-benzene-sulphonyl-thiourea, a compound of the formula

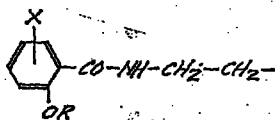


wherein U has the meaning given above, can be converted by treatment with an oxidizing agent in an acid or alkaline medium by simultaneous desulphuration and hydrolysis into the corresponding benzamido-ethyl-benzenesulphonyl-urea.

With regard to the reaction conditions used in the various forms of the process of the invention these may, in general, vary within wide limits and can be adapted to each individual case. For example, the reactions can be carried out with the use of solvents either at room temperature or at an elevated temperature.

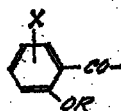
According to the nature of the starting substances, in some cases, one or the other mentioned methods may yield a desired individual benzenesulphonyl-urea in only small amounts or might be inappropriate. Such relatively rare cases can easily be recognized by experts and it is not difficult to use successfully one of the other methods of synthesis described.

As starting substances such compounds are used which contain a benzene nucleus that is substituted by the group

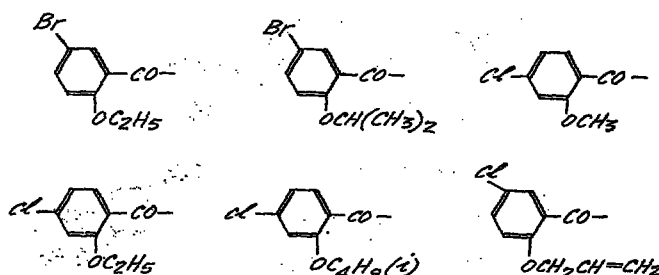


in para-position.

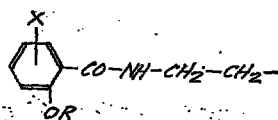
As examples for the part



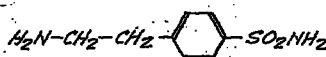
of this substituent there may be mentioned more especially the following



The preparation of the starting substances may be carried out by methods known to be suitable for making such substances. Thus, for example, benzenesulphonamides used as starting substances which are substituted in the benzene nucleus by the radical



can be obtained by reaction of the correspondingly substituted benzene compound with chloro-sulphonic acid and subsequently with ammonia or by acylation of an amino compound of the formula



with a corresponding acid chloride.

The benzenesulphonyl-carbamic acid esters and -ureas used as starting material can be obtained, for example, from a benzenesulphonamide and a halogeno-formic acid alkyl ester or potassium cyanate (KOCN).

The benzenesulphonyl-ureas of the present invention and their physiologically tolerable salts show hypoglycemic properties and are characterised by a strong hypoglycemic action.

The hypoglycemic action can be determined by feeding them to rabbits in doses of 10 mg/kg and determining the blood sugar-value according to the known method by Hagedorn-Jensen or by means of an auto-analyzer over a prolonged period of time.

Thus, it was found, for example, that 10 milligrams/kilogram of N - [4 - (β - <2 - methoxy - 5 - bromo - benzamido> - ethyl) - benzenesulphonyl] - N' - (2,5 - endomethylene - cyclohexyl) - urea provoke, after 3 hours, a lowering of the blood sugar level by 35%, after 24 hours by 26%, and after 48 hours by 18%.

In the same manner, 10 milligrams of N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzene - sulphonyl] - N' - (2,5 - endomethylene - cyclohexyl) - urea provoke after 3 hours a lowering of the blood sugar level of 32%, after 24 hours of 43%, after 48 hours of 28%, and even after 72 hours of 14%, whereas the known N - [4 - methyl - benzene - sulphonyl] - N' - butyl - urea, when administered to rabbits in doses of less than 25 mg/kg, does not provoke a lowering of the blood sugar level.

The strong hypoglycemic action of the benzenesulphonyl-ureas of the present invention becomes more evident if the dose is further reduced. When N - [4 - (β - <2 - methoxy - 5 - bromo - benzamido> - ethyl) - benzenesulphonyl] - N' - (2,5 - endomethylene - cyclohexyl) - urea is administered to rabbits in a dose of 0.01 mg/kg or N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - (2,5 - endomethylene - cyclohexyl) - urea is administered to rabbits in a dose of 0.06 mg/kg, or the N - [4 - (β - <2 - methoxy - 5 - methyl - benzamido> - ethyl) - benzenesulphonyl] - N' - (2,5 - endomethylene - cyclohexyl) - urea is administered to rabbits in a dose of 0.06 mg/kg, a distinct lowering of the blood sugar can still be observed.

The benzenesulphonyl-ureas of the invention are preferably used for the manufacture of pharmaceutical preparations and the invention also provides a pharmaceutical preparation for oral administration and lowering the blood sugar level in the treatment of diabetes mellitus, which comprises a benzenesulphonyl-urea of the invention or a physiologically tolerable salt thereof in admixture or conjunction with a pharmaceutically suitable carrier. Instead of being used in the form of a salt the compounds of the

invention may be used in the presence of a substance which causes such salt formation. For the formation of salts there may be used, for example, bases such, for example, as alkali metal hydroxides or alkaline earth metal hydroxides, alkali metal carbonates or bicarbonates or alkaline earth metal carbonates or bicarbonates.

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

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

The following Examples illustrate the invention:

EXAMPLE 1

N-[4-(β -[<2-methoxy-5-chlorobenzamido>-ethyl]-benzenesulphonyl]-N'-(2,5-endomethylene-cyclohexyl)-urea

4.2 grams of N-[4-(β -[<2-methoxy-5-chlorobenzamido>-ethyl]-benzenesulphonyl]-methyl-urethane (melting point 189—191°C) are suspended in 100 ml of dioxane and after the addition of 1.2 grams of 2,5-endomethylenecyclohexylamine the mixture is heated for about 1 hour to 110°C. When cooling, the N-[4-(β -[<2-methoxy-5-chlorobenzamido>-ethyl]-benzenesulphonyl]-N'-(2,5-endomethylene-cyclohexyl)-urea formed, crystallizes which, after recrystallization from methanol melts at 187—189°C.

In analogous manner there are obtained:

from
N-[4-(β -[<2-methoxy-4-chlorobenzamido>-ethyl]-benzenesulphonyl]-carbamic acid methyl ester (melting point 178—180°C):
N-[4-(β -[<2-methoxy-4-chlorobenzamido>-ethyl]-benzenesulphonyl]-N'-(2,5-endomethylenecyclohexyl)-urea, melting point 203—205°C (from methanol);

from
N-[4-(β -[<2-ethoxy-5-chlorobenzamido>-ethyl]-benzenesulphonyl]-carbamic acid methyl ester (melting point 203—205°C):
N-[4-(β -[<2-ethoxy-5-chlorobenzamido>-ethyl]-benzenesulphonyl]-N'-(2,5-endomethylenecyclohexyl)-urea, melting point 158—160°C (from methanol);

from
N-[4-(β -[<2-methoxy-5-bromobenzamido>-ethyl]-benzenesulphonyl]-carbamic acid methyl ester (melting point 197—199°C):
N-[4-(β -[<2-methoxy-5-bromobenzamido>-ethyl]-benzenesulphonyl]-N'-(2,5-endomethylenecyclohexyl)-urea, melting point 171—172°C (from methanol/dimethylformamide);

from
N-[4-(β -[<2-methoxy-5-methylbenzamido>-ethyl]-benzenesulphonyl]-carbamic acid methyl ester (melting point 175—177°C):
N-[4-(β -[<2-methoxy-5-methylbenzamido>-ethyl]-benzenesulphonyl]-N'-(2,5-endomethylenecyclohexyl)-urea, melting point 191—193°C (from methanol/dimethylformamide);

from
N-[4-(β -[<2,5-dimethoxy-benzamido>-ethyl]-benzenesulphonyl]-carbamic acid methyl ester (melting point 173—175°C):
N-[4-(β -[<2,5-dimethoxy-benzamido>-ethyl]-benzenesulphonyl]-N'-(2,5-endomethylenecyclohexyl)-urea, melting point 163—165°C (from methanol);

from
N-[4-(β -[<-methoxybenzamido>-ethyl]-benzenesulphonyl]-carbamic acid methyl ester (melting point 174—176°C):
N-[4-(β -[<2-methoxybenzamido>-ethyl]-benzenesulphonyl]-N'-(2,5-endomethylenecyclohexyl)-urea, melting point 197—198°C (from methanol);

from

N - [4 - (β - <2 - methoxy - 5 - fluorobenzamido> - ethyl) - benzenesulphonyl] - carbamic acid methyl ester (melting point 171—173°C):

N - [4 - (β - <2 - methoxy - 5 - fluorobenzamido> - ethyl) - benzenesulphonyl] - N' - (2,5 - endomethylenecyclohexyl) - urea, melting point 206—207°C (from methanol/dimethylformamide).

EXAMPLE 2

N-[4-(β -<2-methoxy-5-fluorobenzamido>-ethyl)-benzenesulphonyl]-N'-(2,5-endomethylenecyclohexyl)-urea

6 g of 4 - (β - <2 - methoxy - 5 - fluorobenzamido> - ethyl) - benzenesulphonamide (melting point 167—169°C) are dissolved in 8.5 ml of 2N sodium hydroxide solution and 50 ml of acetone, and 2.5 g of 2,5 - endomethylenecyclohexyl - isocyanate are added dropwise at 0—5°C. Stirring is continued for 3 hours, water and methanol is added, the whole is filtered from the undissolved matter and the filtrate is acidified with dilute hydrochloric acid. The N - [4 - (β - <2 - methoxy - 5 - fluorobenzamido> - ethyl) - benzenesulphonyl] - N' - (2,5 - endomethylenecyclohexyl) - urea which has precipitated, melts after recrystallization from methanol/dimethylformamide at 206—207°C.

In analogous manner there is obtained:

from 4 - (β - <2 - n - propoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonamide (melting point 192—194°C):

4 - (β - <2 - n - propoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonamide N' - (2,5 - endomethylenecyclohexyl) - urea, melting point 171—173°C (from methanol);

from 4 - (β - <2 - n - propoxy - 5 - methylbenzamido> - ethyl) - benzenesulphonamide (melting point 166—167°C):

N - [4 - (β - <2 - n - propoxy - 5 - methylbenzamido> - ethyl) - benzenesulphonyl] - N' - (2,5 - endomethylenecyclohexyl) - urea, melting point 148—150°C (from methanol);

from 4 - (β - <2 - methoxy - 5 - ethylbenzamido> - ethyl) - benzenesulphonamide (melting point 193—195°C):

N - [4 - (β - <2 - methoxy - 5 - ethylbenzamido> - ethyl) - benzenesulphonyl] - N' - (2,5 - endomethylenecyclohexyl) - urea, melting point 162—164°C (from methanol).

EXAMPLE 3

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

2 g of N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - (2,5 - endomethylenecyclohexyl) - thiourea (prepared by boiling for several hours 4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonamide and 2,5 - endomethylenecyclohexyl mustard oil in acetone in the presence of potassium carbonate while stirring, melting point 158—160°C (from dilute methanol)) are dissolved in about 10 ml of 2N sodium hydroxide solution and 5 ml of dioxane. After addition of 5 ml of hydrogen peroxide of 35% strength, the whole is heated for about 20 minutes in a water bath. After cooling it is acidified. There is obtained a crystalline precipitate which is filtered off with suction, dissolved in ammonia of about 1% strength and reprecipitated after filtration by acidification. The thus obtained crude N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzene - sulphonyl] - N' - (2,5 - endomethylenecyclohexyl) - urea melts after recrystallization from methanol at 186—188°C.

EXAMPLE 4

N-[4-(β -<2-methoxy-5-chlorobenzamido>-ethyl)-benzenesulphonyl]-N'-(2,5-endomethylenecyclohexyl)-urea

a) 1 g of N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - N' - (2,5 - endomethylenecyclohexyl) - thiourea (cf. Example 3) is dissolved in 50 ml of ethanol. After addition of 0.5 g of mercury oxide and a small amount of potassium carbonate, the whole is heated to 50—60°C for 4 hours while stirring. It is filtered, concentrated and crystallized from dilute methanol. The thus obtained N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - N' - (2,5 - endomethylenecyclohexyl) - isourea methyl ether melts at 118—120°C.

b) 0.1 g of the product obtained according to 4a), is heated in 2 ml of dioxane and 10 ml of concentrated hydrochloric acid for 20 minutes in a vapour bath. The product

which is obtained after pouring into water is filtered off with suction and recrystallized from dilute methanol. The N - [4 - (β - <2 - methoxy - 5 - chloro - benzenesulphonyl) - N' - (2,5 - endomethylenecyclohexyl) - urea amido> - ethyl] - benzenesulphonyl] - N' - (2,5 - endomethylenecyclohexyl) - urea thus prepared melts at 186—188°C. The same product is obtained by alkaline saponification of the isourea ether prepared according to 4a) by heating for 1 hour with 2N sodium hydroxide solution in a vapour bath.

EXAMPLE 5

N-[4-(β-<2-methoxy-5-chlorobenzamido>-ethyl)-benzenesulphonyl]-
N'-(2,5-endomethylenecyclohexyl)-urea

a) 0.8 g of endomethylenecyclohexyl - parabanic acid (melting point 111—113°C from dilute methanol) is dissolved in 30 ml of benzene, 0.4 g of trimethylamine and 1.6 g of 4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonic acid chloride are added and heated to boil under reflux for 2 1/2 hours. The whole is concentrated *in vacuo*, water is added to the residue obtained and it is triturated. The substance crystallizes after abandoning for some time. It is filtered off with suction, washed with water and recrystallized from methanol/dioxane. The thus obtained 1 - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - 3 - (2,5 - endomethylene - cyclohexyl) - parabanic acid melts at 227—229°C.

b) The product obtained according to 5a) is dissolved in a small amount of dioxane and 2N sodium hydroxide solution and the solution is heated in a vapour bath for 45 minutes. After cooling it is diluted with water and acidified. The precipitate obtained of N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - (2,5 - endomethylenecyclohexyl) - urea melts after recrystallization from methanol/water at 186—188°C.

EXAMPLE 6

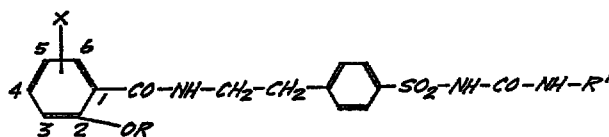
N-[4-(β-<2-methoxy-5-chlorobenzamido>-ethyl)-benzenesulphonyl]-
N'-(2,5-endomethylenecyclohexyl)-urea

a) 3.1 g of N - 2,5 - endomethylenecyclohexyl - urea are dissolved in pyridine, when introducing 7.4 g of 4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl chloride slight heating occurs. The clear solution is added after 10 minutes to a mixture of ice water and dilute hydrochloric acid, the precipitate thus formed is filtered off with suction, and stirred with ammonia of 0.5% strength. The amorphous precipitate is dissolved in acetone while hot. When cooling, the N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzene - sulphonyl] - N' - (2,5 - endomethylenecyclohexyl) - urea crystallizes, having a melting point of 133—135°C.

b) 1 g of the above-mentioned urea is dissolved in 20 ml of dimethyl-formamide and an aqueous potassium permanganate solution in excess is added to the bath. After filtration of the pyrolusite, water and dilute hydrochloric acid is added and the precipitate which has formed is recrystallized. There is obtained N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - N' - (2,5 - endomethylenecyclohexyl) - urea melting at 187—189°C.

WHAT WE CLAIM IS:—

1. Benzenesulphonyl-ureas corresponding to the formula



in which

R represents a lower alkyl or lower alkenyl radical,
X represents a hydrogen, fluorine, chlorine or bromine atom, or a lower alkyl or lower alkoxy radical in the 4- or 5-position relative to the carbonamide group,
and

R¹ represents an endomethylene-cyclohexenyl, endomethylene-cyclohexyl, endoethylene-cyclohexyl or endoethylene-cyclohexenyl radical.

2. A compound as claimed in claim 1, wherein R is methyl, X is chlorine in 5-position and R¹ is 2,5-endomethylene-cyclohexyl.

3. A compound as claimed in claim 1, wherein R is methyl, X is bromine in 5-position and R¹ is 2,5-endomethylene-cyclohexyl.

which is obtained after pouring into water is filtered off with suction and recrystallized from dilute methanol. The N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - (2,5 - endomethylenecyclohexyl) - urea thus prepared melts at 186—188°C. The same product is obtained by alkaline saponification of the isourea ether prepared according to 4a) by heating for 1 hour with 2N sodium hydroxide solution in a vapour bath.

EXAMPLE 5

N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - N' - (2,5 - endomethylenecyclohexyl) - urea

- 10 a) 0.8 g of endomethylenecyclohexyl - parabanic acid (melting point 111—113°C from dilute methanol) is dissolved in 30 ml of benzene, 0.4 g of trimethylamine and 1.6 g of 4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonic acid chloride are added and heated to boil under reflux for 2 1/2 hours. The whole is concentrated *in vacuo*, water is added to the residue obtained and it is triturated.
- 15 The substance crystallizes after abandoning for some time. It is filtered off with suction, washed with water and recrystallized from methanol/dioxane. The thus obtained 1 - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - 3 - (2,5 - endomethylene - cyclohexyl) - parabanic acid melts at 227—229°C.
- 20 b) The product obtained according to 5a) is dissolved in a small amount of dioxane and 2N sodium hydroxide solution and the solution is heated in a vapour bath for 45 minutes. After cooling it is diluted with water and acidified. The precipitate obtained of N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - (2,5 - endomethylenecyclohexyl) - urea melts after recrystallization from methanol/water at 186—188°C.

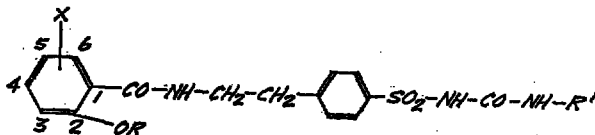
EXAMPLE 6

N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - N' - (2,5 - endomethylenecyclohexyl) - urea

- 25 a) 3.1 g of N - 2,5 - endomethylenecyclohexyl - urea are dissolved in pyridine, when introducing 7.4 g of 4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl chloride slight heating occurs. The clear solution is added after 10 minutes to a mixture of ice water and dilute hydrochloric acid, the precipitate thus formed is filtered off with suction, and stirred with ammonia of 0.5% strength. The amorphous precipitate is dissolved in acetone while hot. When cooling, the N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzene - sulphonyl] - N' - (2,5 - endomethylenecyclohexyl) - urea crystallizes, having a melting point of 133—135°C.
- 30 b) 1 g of the above-mentioned urea is dissolved in 20 ml of dimethyl-formamide and an aqueous potassium permanganate solution in excess is added to the bath. After filtration of the pyrolusite, water and dilute hydrochloric acid is added and the precipitate which has formed is recrystallized. There is obtained N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - N' - (2,5 - endomethylenecyclohexyl) - urea melting at 187—189°C.

WHAT WE CLAIM IS:—

1. Benzenesulphonyl-ureas corresponding to the formula



in which

- R represents a lower alkyl or lower alkenyl radical,
 X represents a hydrogen, fluorine, chlorine or bromine atom, or a lower alkyl or lower alkoxy radical in the 4- or 5-position relative to the carbonamide group, and
 R¹ represents an endomethylene-cyclohexenyl, endomethylene-cyclohexyl, endoethylene-cyclohexyl or endoethylene-cyclohexenyl radical.

2. A compound as claimed in claim 1, wherein R is methyl, X is chlorine in 5-position and R¹ is 2,5-endomethylene-cyclohexyl.

3. A compound as claimed in claim 1, wherein R is methyl, X is bromine in 5-position and R¹ is 2,5-endomethylene-cyclohexyl.



4. A compound as claimed in claim 1, wherein R is methyl X is methyl in 5-position and R¹ is 2,5-endomethylene-cyclohexyl.

5. A compound as claimed in claim 1, wherein R is methyl, X is chlorine in 4-position and R¹ is 2,5-endomethylene-cyclohexyl.

6. A compound as claimed in claim 1, wherein R is ethyl, X is chlorine in 5-position and R¹ is 2,5-endomethylene-cyclohexyl.

7. A compound as claimed in claim 1, wherein R is methyl, X is methoxy in 5-position and R¹ is 2,5-endomethylene-cyclohexyl.

8. A compound as claimed in claim 1, wherein R is methyl, X is hydrogen and R¹ is 2,5-endomethylene-cyclohexyl.

9. A compound as claimed in claim 1, wherein R is methyl, X is fluorine in 5-position and R¹ is 2,5-endomethylene-cyclohexyl.

10. A compound as claimed in claim 1, wherein R is n-propyl, X is chlorine in 5-position and R¹ is 2,5-endomethylene-cyclohexyl.

11. A compound as claimed in claim 1, wherein R is n-propyl, X is methyl in 5-position and R¹ is 2,5-endomethylene-cyclohexyl.

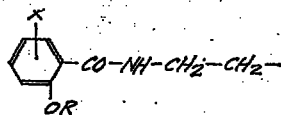
12. A compound as claimed in claim 1, wherein R is methyl, X is ethyl in 5-position and R¹ is 2,5-endomethylene-cyclohexyl.

13. Any one of the compounds claimed in claim 1 and which is described in the Examples herein.

14. Physiologically tolerable salts of any one of the compounds claimed in any one of claims 1 to 13.

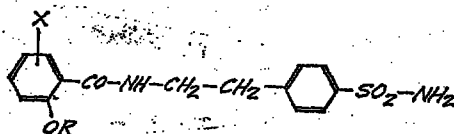
15. A process for the manufacture of benzenesulphonyl-ureas as claimed in claim 1, wherein

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



is reacted with an amine, R'-NH₂, or a salt thereof;

b) a sulphonamide of the formula



or a salt thereof is reacted with an R¹-isocyanate, an R¹-substituted-carbamic acid ester, -thiolcarbamic acid ester, -carbamic acid halide or -urea;

c) a correspondingly substituted benzenesulphonyl-isourea ether, benzenesulphonyl-isourea ester, benzenesulphonyl-isothiurea ether, benzenesulphonyl-parabanic acid or benzenesulphonyl-haloformic acid amidine is hydrolyzed;

d) a correspondingly substituted benzenesulphonyl-halide is reacted with an R¹-substituted urea or an alkali metal salt thereof;

e) a correspondingly substituted benzenesulphinic acid halide or, in the presence of an acid condensing agent a correspondingly substituted benzenesulphinic acid or an alkali metal salt thereof, is reacted with a hydroxy urea the NH₂ group of which is substituted by R¹;

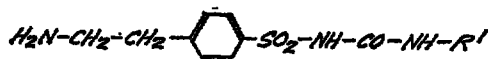
f) a correspondingly substituted carbodiimide is treated with water.

g) in a correspondingly substituted benzenesulphonyl-thio-urea the sulphur atom is exchanged for an oxygen atom;

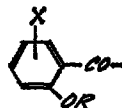
h) a correspondingly substituted benzenesulphinyl-urea or benzenesulphenyl-urea is oxidized;



- i) a corresponding benzenesulphonyl-urea containing in the molecule an unsaturated linkage is hydrogenated;
j) in a benzenesulphonyl-urea of the formula

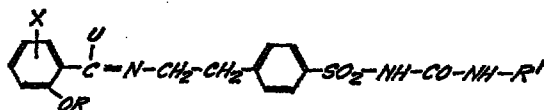


5 the radical

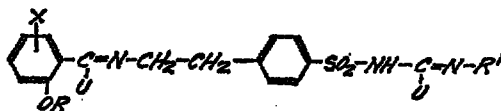


is introduced by acylation, if desired in several stages;

- k) in a correspondingly substituted thiobenzamido-ethyl-benzenesulphonyl-urea or -benzenesulphonyl-thiourea the sulphur atom or the sulphur atoms are exchanged 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



15 wherein U represents O-lower alkyl, S-lower alkyl or a halogen atom (preferably chlorine) is saponified and, if a salt is desired, the reaction product is treated with a base, R, R' and X are as defined in claim 1.

16. A process as claimed in claim 15, conducted substantially as described in any one of the Examples herein.

20 17. 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 14 in admixture or conjunction with a pharmaceutically suitable carrier.

25 18. A pharmaceutical preparation as claimed in claim 17, which contains in dosage unit form from 2 to 10 milligrammes of the active ingredient.

19. A pharmaceutical preparation as claimed in claims 17 or 18 which is in the form of a tablet.

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

Reference has been directed in pursuance of Section 9, Sub-Section (1) of the Patents Act, 1949, to patent No. 1,080,705.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1970.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

