

PATENT SPECIFICATION

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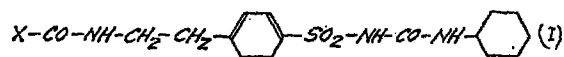


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(54) BENZENESULPHONYL UREAS AND PROCESS FOR THEIR MANUFACTURE

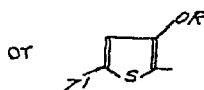
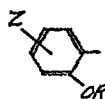
(71) We, FARBWERKE HOECHST AKTIENGESELLSCHAFT, vormals Meister Lucius & Brüning, a Company recognized by German Law, of 6230 Frankfurt (Main) 80, Postfach 80 03 20, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed to be particularly described in and by the following statement:—

The present invention provides benzenesulphonyl-ureas of the general formula



in which

X represents



wherein

R stands for an alkyl group having 1 to 4 carbon atoms,

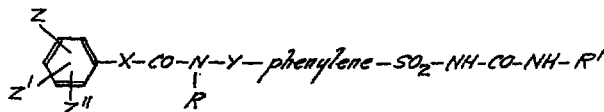
Z stands for a halogen atom or an alkyl or alkoxy group both having 1 to 4 carbon atoms, and

Z' stands for a halogen atom or an alkyl group having 1 to 4 carbon atoms.

The invention also provides salts of such compounds. The compounds of the above general formula are new and in their free form or in the form of their physiologically tolerable salts exhibit blood sugar lowering properties and are distinguished by a strong and long lasting hypoglycemic action.

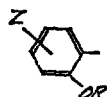
Specification No. 1,080,705 discloses inter alia compounds of the general formula

[Price 25p]



in which R represents a hydrogen atom, R' represents a cyclohexenyl group, X represents a single chemical bond, Y represents a hydrocarbon group containing 1 to 4 carbon atoms, Z represents a halogen atom, or an alkyl or alkoxy group, both having 1 to 4 carbon atoms, Z' represents a hydrogen atom and Z'' represents an alkoxy group containing 1 to 4 carbon atoms.

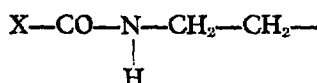
As compared with the comparable compounds disclosed in that specification, the compounds of the present invention in which X represents



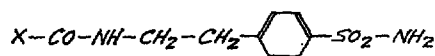
have a hypoglycemic action which is significantly stronger and more long lasting.

The present invention also provides a process for the manufacture of these benzenesulphonyl-ureas, wherein

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

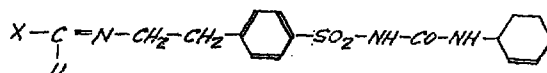


is reacted with Δ2-cyclohexenyl-amine or salt thereof, or a sulphonamide of the formula

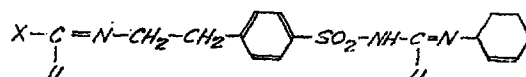


or a salt thereof is reacted with Δ2-cyclohexenyl isocyanate or with a Δ2-cyclohexenyl-carbamic acid ester, -thiolcarbamic acid ester, -carbamic acid halide or -urea;

- b) a correspondingly substituted benzenesulphonyl-isourea ether, benzenesulphonyl-isourea ester, benzenesulphonyl-isothiurea ether, benzenesulphonyl-aparabanic acid or benzenesulphonyl-haloformic acid amidine is hydrolysed, or a compound of the formula



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

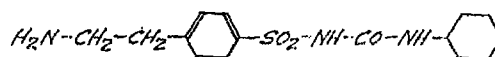


wherein U stands for oxygen-lower-alkyl, sulphur-lower-alkyl or halogen (preferably chlorine), is saponified, or water is added to a correspondingly substituted carbodiimide;

- c) in a correspondingly substituted benzenesulphonyl-thiourea or thioamido-alkyl-benzenesulphonyl-urea, the sulphur atom is replaced by an oxygen atom;
d) a correspondingly substituted benzenesulphonyl-urea or benzenesulphenyl-urea is oxidized;
e) the group



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



- 5 f) a correspondingly substituted benzenesulphonyl halide is reacted with Δ^2 -cyclohexenyl-urea or an alkali metal salt thereof; or
a correspondingly substituted benzenesulphinic acid halide or, in the presence of an acid condensation agent, even a correspondingly substituted benzenesulphinic acid or alkali metal salt thereof is reacted with N- Δ^2 -cyclohexenyl-N'-hydroxy-urea;

10 and, where required, the reaction product so obtained is treated with a base for salt formation.

The aforesaid benzenesulphonyl-carbamic acid esters or benzene-sulphonyl-thiol-carbamic acid esters may have in the alcoholic component an alkyl group or an aryl group or even a heterocyclic radical. Since this radical 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 Δ^2 -cyclohexenylamine-substituted carbamic acid esters and the corresponding thiolcarbamic acid esters.

As carbamic acid halides, the chlorides are preferably used.

20 The benzenesulphonyl-ureas used as starting materials in the process of the present invention may be unsubstituted at the nitrogen atom of the urea molecule not joined to the sulphonyl group or may be mono- or especially di-substituted. Since these substituents are split off during the reaction with the amines, 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 benzenesulphonyl-carbamoyl-imidazoles and similar compounds or bis-(benzenesulphonyl)-ureas which may carry at one of the nitrogen atoms a further substituent, for example, a methyl group. For example, such a bis-(benzenesulphonyl)-urea or N-benzenesulphonyl-N'-acyl-urea may be treated with Δ^2 -cyclohexenylamine and the salt so obtained may be heated to elevated temperatures, especially to a temperature above 100°C.

30 Furthermore, it is possible to start from a Δ^2 -cyclohexenyl-urea or from Δ^2 -cyclohexenyl-urea which is mono- or especially di-substituted at the available nitrogen atom and to react it with a benzenesulphonamide carrying the substituent



35 in para-position. As such starting materials, there may be used for example N- Δ^2 -cyclohexenyl-urea, the corresponding N'-acetyl, N'-nitro- N'- Δ^2 -cyclohexenyl, N';N'-diphenyl (in which case the two phenyl radicals may also be substituted or be linked with each other either directly or by means of a bridge member such, for example, as $-CH_2-$, $-NH-$, $-O-$ or $-S-$), N'-methyl-N'-phenyl, N',N'-dicyclohexyl-ureas as well as Δ^2 -cyclohexenyl-carbamoyl-imidazoles, -pyrazoles or -triazoles.

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

45 The replacement of the sulphur atom in the correspondingly substituted benzene-sulphonyl-thioureas by an oxygen atom can be effected in known manner, for example, with the aid of oxides or salts of heavy metals or with the use of oxidizing agents such, for example, as hydrogen peroxide, sodium peroxide, nitrous acid or permanganates.

50 The thioureas may also be desulphurized by treatment with phosgene or phosphorus pentachloride. The chloroformic acid amidines or chloroformic acid carbodiimides obtained as intermediates may be converted into the benzenesulphonylureas by suitable measures such, for example, as by saponification or addition of water.

55 The acylation of aminoethyl-benzenesulphonyl-ureas may be carried out either in one step, for example, by the reaction of correspondingly substituted benzoic acid halides, 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 aminoethyl-benzenesulphonyl-ureas with 2-methoxy-benzoyl chloride and the subsequent intro-

duction of a halogen atom into the benzene nucleus of the benzamido group.

The oxidation of the benzenesulphonyl-ureas or benzene-sulphenyl-ureas may be carried out with the aid of known oxidizing agents, for example potassium permanganate.

As regards the reaction conditions, the variations of carrying out the process of the invention may, in general, be modified within wide limits and can be 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 aforesaid methods 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 starting materials are prepared by methods that are generally known. For example, substituted benzene-sulphonamides used as starting substances may be obtained by the reaction of the corresponding benzene compounds with chlorosulphonic acid and subsequently with ammonia or by acylation of *p*-aminoethyl-benzenesulphonamide with a corresponding acid chloride. The benzenesulphonyl-urethanes or benzene-sulphonyl-ureas used as starting materials may be prepared, for example, from the corresponding benzenesulphonamides and haloformic acid alkyl esters or potassium cyanate (KOCN). Benzenesulphonyl-ureas or benzenesulphenyl-ureas may be obtained by the condensation of the corresponding sulphonyl chlorides or sulphenyl chlorides with ureas.

The hypoglycemic action of the benzenesulphonyl-ureas of the invention can be ascertained by administering them to normally fed rabbits in the form of the sodium salts in a dose 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 auto-analyzer for a prolonged period of time.

Thus, it has been established that N-[4-(β -2-methoxy-5-chlorobenzamido)-ethyl]-benzenesulphonyl]-N'-(Δ 2-cyclohexenyl)-urea (I) causes the lowering of the blood sugar as indicated in the following Table.

For comparison, the Table also shows the lowering of the blood sugar level obtained with the known N[4-(β -2-methoxy-5-chlorobenzamido)-ethyl]-benzenesulphonyl]-N'-cyclohexyl-urea (II).

TABLE

Lowering of the blood sugar level of rabbits, in %, after oral administration of 10 mg/kg

after	1	3	6	24	48	72	96	120	hours
Compound I	32	25	24	27	36	36	25	0	
Compound II	—	19	—	23	28	13	0	—	

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 as alkali metal or alkaline earth metal hydroxides and alkali metal or alkaline earth metal carbonates or bicarbonates.

The present invention also provides a pharmaceutical preparation for oral administration and lowering the blood sugar level in the treatment of diabetes mellitus, which comprises a compound of the general formula (1) or a physiologically tolerable salt thereof in admixture or conjunction with a pharmaceutically suitable carrier.

The pharmaceutical preparations of the invention are preferably made up in the form of tablets and as pharmaceutically suitable carriers there may be mentioned, for example, talc, starch, lactose, tragacanth and 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 or more of the aforementioned carriers, is advantageously brought into a suitable dosage unit form. The dose chosen should comply with the activity of the benzenesulphonyl-urea used and with the desired effect. Advantageously, the dosage per unit amounts to 0.5 to 100 mg, preferably 2

to 10 mg, but considerably higher or lower dosage units may also be used, which, when required, are divided or multiplied prior to their administration.

The following Examples illustrate the invention:—

EXAMPLE 1

5 N-[4-(β-(2-methoxy-5-methylbenzamido)-ethyl)-benzenesulphonyl]-N'-(Δ2-cyclohexenyl)-urea 5

7 g of N-[4-(β-(2-methoxy-5-methylbenzamido)-ethyl)-benzenesulphonyl]-methylurethane (m.p. 175—177°C) were suspended in 200 ml of xylene and at 80°C 1.9 g of Δ2-cyclohexenylamine were added thereto. After a short time, the temperature of the oil bath was raised to 150°C and this temperature was maintained for 30 minutes. The reaction mixture was dissolved and methanol distilled off. When cooling, the N-[4-(β-(2-methoxy-5-methylbenzamido)-ethyl)-benzenesulphonyl]-N'-(Δ2-cyclohexenyl)-urea precipitated in the form of crystals and melted at 194—196°C, after recrystallization from methanol/dimethylformamide. 15

EXAMPLE 2

20 N-[4-(β-(2-methoxy-5-chlorobenzamido)-ethyl)-benzenesulphonyl]-N'-(Δ2-cyclohexenyl)-urea 20

2.45 g of N-[4-(β-(2-methoxy-5-chlorobenzamido)-ethyl)-benzenesulphonyl]-phenylurethane (obtained from 4-[β(2-methoxy-5-chlorobenzamido)-ethyl]-benzenesulphonamide and chloroformic acid phenyl ester) were refluxed for 2 hours with 0.5 g of Δ2-cyclohexenylamine in 30 ml of dioxane. After dilution with water and acidification with dilute hydrochloric acid a precipitate was obtained which was treated with 0.5% ammonia. The aqueous alkaline solution was acidified and the precipitate obtained was recrystallized from methanol N-[4-(β-(2-methoxy-5-chlorobenzamido)-ethyl)-benzenesulphonyl]-N'-(Δ2-cyclohexenyl)-urea, melting point 169—170°C, was obtained. 25

EXAMPLE 3

30 N-[4-(β-(2-methoxy-5-chlorobenzamido)-ethyl)-benzenesulphonyl]-N'-(Δ2-cyclohexenyl)-urea 30

4.26 g of N-[4-(β-(2-methoxy-5-chlorobenzamido)-ethyl)-benzenesulphonyl]-methylurethane were heated for one and a half hours with 1.6 g of Δ2-cyclohexenylamine acetate in 100 ml of dioxane using a descending condenser.

After addition of water and recrystallization of the product obtained from methanol N-[4-(β-(2-methoxy-5-chlorobenzamido)-ethyl)-benzenesulphonyl]-N'-(Δ2-cyclohexenyl)-urea melting at 169—170°C, was obtained in a very good yield. 35

In an analogous manner there were obtained:

40 N-[4-(β-(2-methoxy-5-bromobenzamido)-ethyl)-benzenesulphonyl]-N'-(Δ2-cyclohexenyl)-urea, melting point 175—177°C (from ethanol), 40

N-[4-(β-(4-chloro-2-methoxy-benzamido)-ethyl)-benzenesulphonyl]-N'-(Δ2-cyclohexenyl)-urea, melting point 170°C (from water/ethanol),

N-[4-(β-(2-methoxy-4-methylbenzamido)-ethyl)-benzenesulphonyl]-N'-(Δ2-cyclohexenyl)-urea, melting point 188—190°C (from ethanol), 45

N-[4-(β-(2-ethoxy-5-chlorobenzamido)-ethyl)-benzenesulphonyl]-N'-(Δ2-cyclohexenyl)-urea, melting point 175—177°C (from water/ethanol), 45

N-[4-(β-(2-ethoxy-5-methylbenzamido)-ethyl)-benzenesulphonyl]-N'-(Δ2-cyclohexenyl)-urea, melting point 159—161°C (from water/ethanol),

N-[4-(β-(2-ethoxy-4-chlorobenzamido)-ethyl)-benzenesulphonyl]-N'-(Δ2-cyclohexenyl)-urea, melting point 148—150°C (from ethanol), 50

N-[4-(β-(2-ethoxy-4-methylbenzamido)-ethyl)-benzenesulphonyl]-N'-(Δ2-cyclohexenyl)-urea, melting point 150—152°C (from ethanol) and N-[4-(β-(5-chloro-3-methoxy-thiophene-2-carbonamido)-ethyl)-benzenesulphonyl]-N'-(Δ2-cyclohexenyl)-urea, melting point 166—168°C (from water/ethanol). 55

EXAMPLE 4

60 N-[4-(β-(2-methoxy-5-chlorobenzamido)-ethyl)-benzenesulphonyl]-N'-(Δ2-cyclohexenyl)-urea 60

A mixture of 10.3 g of N-[4-(β-(2-methoxy-5-chlorobenzamido)-ethyl)-benzenesulphonyl]-urea (m.p. 171—173°C), 300 ml of toluene, 30 ml of glycolmonomethyl ether, 1.65 g of glacial acetic acid and 2.8 g of Δ2-cyclohexenylamine was refluxed for

5 hours. Subsequently the mixture was concentrated *in vacuo* and the residue was treated with alcohol. N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - N' - (Δ2 - cyclohexenyl) - urea obtained as a raw product was suction-filtered and recrystallized from methanol. Melting point 167—169°C.

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EXAMPLE 5

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N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - N' - (Δ2 - cyclohexenyl) - urea

4.9 g of N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - N' - phenyl - urea (m.p. 193—195°C), 100 ml of dioxane and 1 g. of Δ2-cyclohexenylamine were refluxed for 1 hour. The clear solution was subsequently concentrated *in vacuo* and the residue obtained was treated with about 0.5% - ammonia. After clarification of the solution by filtration it was acidified. The precipitate of N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - N' - (Δ2 - cyclohexenyl) - urea obtained was suction-filtered and dried. After recrystallization from methanol a product was obtained having the melting point of 169—170°C.

EXAMPLE 6

N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - N' - (Δ2 - cyclohexenyl) - urea

2.3 g of N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - N' - acetyl - urea (m.p. 208 with decomposition) and 0.5 g of Δ2-cyclohexenylamine were carefully mixed. Upon heating, the cyclohexenylamine salt of N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - N' - acetyl - urea was formed. The salt was heated to 150°C for 45 minutes in an Erlenmeyer flask immersed in an oil bath. After several minutes the salt melted to form a clear melt.

The melt was cooled, treated with aqueous 0.5% - ammonia while heating on the steam bath, then filtered and the filtrate was acidified. The precipitated crystals were suction-filtered and taken up once more in 0.5% - ammonia.

Upon acidification of the filtrate, a crystalline precipitate of N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - N' - (Δ2 - cyclohexenyl) - urea was obtained, suction-filtered and dried. After recrystallization from methanol the substance melted at 167—169°C.

EXAMPLE 7

N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - N' - (Δ2 - cyclohexenyl) - urea

6.5 g of sodium salt of 4 - [β - (2 - methoxy - 5 - chlorobenzamido) - ethyl] - benzenesulphonamide were refluxed for 3 hours with 3.9 g of diphenylcarbamic acid chloride in 60 ml of toluene. The crude N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - N'N' - diphenyl - urea obtained was suction-filtered, suspended in dioxane and, after addition of 1g of acetic acid and 1.8 g of Δ2-cyclohexenyl-amine the substance was refluxed for 1½ hours. After acidification with dilute hydrochloric acid the precipitate was suction-filtered and treated with 0.5% - ammonia. The aqueous alkaline solution was acidified and the crystals were re-crystallized from methanol.

N[4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - N' - (Δ2 - cyclohexenyl) - urea was obtained having a melting point of 167—169°C.

EXAMPLE 8

N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - N' - (Δ2 - cyclohexenyl) - urea

0.95 g of N,N' - bis - 4 - [β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - urea (m.p. 183—185°C) were suspended in 30 ml of dioxane. 0.125 g Δ2-cyclohexenylamine were added and the whole was refluxed for 1 hour. After concentration of the clear solution obtained the residue was treated with 0.5% - aqueous ammonia, 4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonamide obtained was separated by filtration and acidified. A crystallized precipitate of N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - N' - (Δ2 - cyclohexenyl) - urea was obtained, suction-filtered, dried and recrystallized from methanol. Melting point 166—169°C.

EXAMPLE 9

N-[4-(β-⟨2-methoxy-5-chlorobenzamido⟩-ethyl)-benzenesulphonyl]-
N'-(Δ2-cyclohexenyl)-urea

- 5 4.95 g of 4 - [4 - (β - ⟨2 - methoxy - 5 - chlorobenzamido⟩ - ethyl) - benzene-
sulphonyl] - 1,1 - pentamethylenesemicarbazide, melting point 165—167°C, 50 ml 5
of dioxane and 1 g of Δ2-cyclohexenylamine were refluxed for 45 minutes. The solu-
tion obtained was concentrated *in vacuo* and the residue was taken up in about 0.5%-
aqueous ammonia. The solution was filtered and the filtrate was acidified. A crystal-
line precipitate of N - [4 - (β - ⟨2 - methoxy - 5 - chlorobenzamido⟩ - ethyl) - ben-
zenesulphonyl] - N' - (Δ2 - cyclohexenyl) - urea was obtained, suction-filtered and 10
dried. After recrystallization from methanol the substance melted at 167—169°C. 10

EXAMPLE 10

N-[4-(β-⟨2-methoxy-5-chlorobenzamido⟩-ethyl)-benzenesulphonyl]-N'-
(Δ2-cyclohexenyl)-urea

- 15 1.8 g 4 - [4 - (β - ⟨2 - methoxy - 5 - chlorobenzamido⟩ - ethyl) - benzene-
sulphonyl] - cyclooctanone - semicarbazone, 50 ml of dioxane and 0.33 g of Δ2-cyclo- 15
hexenylamine were refluxed for 1 hour. The clear solution was concentrated *in vacuo*
and the residue obtained was treated with about 0.5%-aqueous ammonia. After filtra-
tion the filtrate was acidified. A crystalline precipitate of N - [4 - (β - ⟨2 - methoxy-
5 - chlorobenzamido⟩ - ethyl) - benzenesulphonyl] - N' - (Δ2 - cyclohexenyl) - urea 20
was obtained, suction-filtered, dried and recrystallized from methanol. The melting
point of the substance was about 167—169°C. 20

EXAMPLE 11

N-[4-(β-⟨2-methoxy-5-chlorobenzamido⟩-ethyl)-benzenesulphonyl]-N'-(Δ2-
cyclohexenyl)-urea

- 25 7.5 g of 4 - (β - ⟨2 - methoxy - 5 - chlorobenzamido⟩ - ethyl) - benzenesulphon-
amide and 5.6 g of ground potassium carbonate were suspended in 150 ml of acetone
and refluxed for 3 hours. Subsequently, 2.6 g of Δ2-cyclohexenyl-isocyanate (prepared
by thermal decomposition of N-(Δ2-cyclohexenyl)-N',N'-diphenyl-urea, boiling point 30
54°C under a pressure of 12 mm mercury) were added thereto and the whole was
heated for another 5 hours. The precipitate formed was suction-filtered, suspended
in water and acidified with dilute hydrochloric acid. After suction-filtration N - [4-
(β - ⟨2 - methoxy - 5 - chlorobenzamido⟩ - ethyl) - benzenesulphonyl] - N' - (Δ2-
cyclohexenyl) - urea was obtained which after recrystallization from methanol melted 35
at 169—170°C. 35

EXAMPLE 12

N-[4-(β-⟨2-methoxy-5-chlorobenzamido⟩-ethyl)-benzenesulphonyl]-N'-(Δ2-
cyclohexenyl)-urea

- 40 3.9 g of 4 - (β - ⟨2 - methoxy - 5 - chlorobenzamido⟩ - ethyl) - benzenesulphon-
amide sodium and 4.4 g of N-(Δ2-cyclohexenyl)-carbamic-acid phenyl ester (prepared
from chloroformic acid phenyl ester and Δ2-cyclohexenylamine, m.p. 114—116°C)
were dissolved in 100 ml of dimethylformamide. The solution was heated to 110°C
for 45 minutes, then cooled and poured in about 0.5%-aqueous ammonia. Undis-
solved substance was separated by filtration and the filtrate was acidified. The crys-
tallized precipitate of N - [4 - (β - ⟨2 - methoxy - 5 - chlorobenzamido⟩ - ethyl)- 45
benzenesulphonyl] - N' - (Δ2 - cyclohexenyl) - urea which had precipitated was suc-
tion-filtered, washed and dried. After recrystallization from methanol the substance
melted at 167—169°C. 45

EXAMPLE 13

N-[4-(β-⟨2-methoxy-5-chlorobenzamido⟩-ethyl)-benzenesulphonyl]-N'-(Δ2-
cyclohexenyl)-urea

- 50 3.9 g of 4-(β-⟨2-methoxy-5-chlorobenzamido⟩-ethyl)-benzenesulphonamide sodium
and 4.26 g of Δ2-cyclohexenyl-urea (m.p. 191—193°C) were carefully mixed in a
mortar and heated to 200°C for 10 minutes in an Erlenmeyer flask immersed in a
pre-heated oil bath. After cooling the melt was heated on a steam bath with about 55
0.5%-ammonia. The substance was filtered and the filtrate was acidified. The pre-
cipitate obtained was suction-filtered and taken up once more in 0.5%-ammonia.
After another acidification of the filtrate the precipitate obtained was suction-filtered,
dried and re-crystallized from methanol. 55
N - [4 - (β - ⟨2 - methoxy - 5 - chlorobenzamido⟩ - ethyl) - benzenesulphonyl]- 60
N' - (Δ2 - cyclohexenyl) - urea obtained melted at 165—167°C. 60

EXAMPLE 14

N-[4-(β-(2-methoxy-5-chlorobenzamido)-ethyl)-benzenesulphonyl]-N'-(Δ2-cyclohexenyl)-urea

5 3.9 g 4-(β-(2-methoxy-5-chlorobenzamido)-ethyl)-benzenesulphonamide sodium and 3.7 g of N-acetyl-N'-(Δ2-cyclohexenyl)-urea (m.p. 102—104°C, prepared from Δ2-cyclohexenyl-urea and acetic anhydride) were heated to 110°C for 2 hours in 100 ml of dimethylformamide. The solution obtained was concentrated under reduced pressure to 2/3 of its volume and then water and hydrochloric acid were added thereto. The substance was suction-filtered and the residue was treated with 0.5% aqueous ammonia. After filtration the filtrate was acidified and the precipitate obtained was suction-filtered, washed and dried. After recrystallization from methanol N-[4-(β-(2-methoxy-5-chlorobenzamido)-ethyl)-benzenesulphonyl]-N'-(Δ2-cyclohexenyl)-urea was obtained having a melting point of 168—170°C.

EXAMPLE 15

N-[4-(β-(2-methoxy-5-chlorobenzamido)-ethyl)-benzenesulphonyl]-N'-(Δ2-cyclohexenyl)-urea

15 3.9 g of 4-(β-(2-methoxy-5-chlorobenzamido)-ethyl)-benzenesulphonamide sodium, 5.9 g of N,N-diphenyl-N'-(Δ2-cyclohexenyl)-urea (m.p. 132—134°C, prepared from diphenyl carbamic acid chloride and Δ2-cyclohexenylamine) and 10 ml of dimethylformamide were heated to 110°C for 45 minutes. (After several minutes a clear solution was obtained). The solution was cooled, poured into water and then 0.5% ammonia was added thereto. After filtration the filtrate was acidified, the precipitate obtained was suction-filtered and introduced once more into 0.5% ammonia. After filtration and acidification of the filtrate a crystalline precipitate of N-[4-(β-(2-methoxy-5-chlorobenzamido)-ethyl)-benzenesulphonyl]-N'-(Δ2-cyclohexenyl)-urea was obtained which, after drying and recrystallization from methanol, melted at 169—170°C.

EXAMPLE 16

N-[4-(β-(2-methoxy-5-chlorobenzamido)-ethyl)-benzenesulphonyl]-N'-(Δ2-cyclohexenyl)-urea

30 2 g of 4-(β-(2-methoxy-5-chlorobenzamido)-ethyl)-benzenesulphonamide sodium and 2.5 g of N,N'-di-(Δ2-cyclohexenyl)-urea (m.p. 239—241°C, prepared from Δ2-cyclohexenylisocyanate and Δ2-cyclohexenylamine) were carefully mixed in a mortar. The mixture was heated to 220°C for 10 minutes in an Erlenmeyer flask immersed in a pre-heated oil bath. After cooling the sintered reaction cake was treated with 0.5% ammonia. After filtration the filtrate was acidified and a precipitate was obtained which was suction-filtered and taken up once more in 0.5% ammonia. The precipitate of crude N-[4-(β-(2-methoxy-5-chlorobenzamido)-ethyl)-benzenesulphonyl]-N'-(Δ2-cyclohexenyl)-urea obtained was suction-filtered and dried. Upon treating it with methanol an at first smeary and then crystalline substance was obtained, which after suction-filtration, was once more recrystallized from methanol. The melting point of N-[4-(β-(2-methoxy-5-chlorobenzamido)-ethyl)-benzenesulphonyl]-N'-(Δ2-cyclohexenyl)-urea obtained was 168—169°C.

EXAMPLE 17

N-[4-(β-(2-methoxy-5-chlorobenzamido)-ethyl)-benzenesulphonyl]-N'-(Δ2-cyclohexenyl)-urea

45 a) Potassium salt of N-[4-(β-(2-methoxy-5-chlorobenzamido)-ethyl)-benzenesulphonyl]-iminodithio-carbonic acid. 74 g of 4-(β-(2-methoxy-5-chlorobenzamido)-ethyl)-benzenesulphonamide were dissolved in 350 ml of dimethylformamide. While stirring 23 g of carbon disulphide and subsequently a solution of 34 g of potassium hydroxide in 50 ml of water were added thereto dropwise. Stirring was continued for 3 hours at room temperature and the clear solution obtained was poured into 4 l of ethanol. The potassium salt of N-[4-(β-(2-methoxy-5-chlorobenzamido)-ethyl)-benzenesulphonyl]-iminodithio-carbonic acid which had precipitated was suction-filtered, washed with alcohol and dried. Yield 60 g.

60 b) N-[4-(β-(2-methoxy-5-chlorobenzamido)-ethyl)-benzenesulphonyl]-iminodithio-carbonic acid dimethyl ester. 36 g of the potassium salt obtained according to a) were dissolved in 60 ml of 1-normal sodium hydroxide solution. While shaking 12.6 g of dimethyl sulphate were added to the clear solution, whereupon the temperature of the solution rose. After standing for 30 minutes a semi-

solid smeary precipitate was separated by decanting. After washing with water, the smeary precipitate crystallized. The crystalline substance was recrystallized from dilute methanol and 30 g of N-[4-(β -<2-methoxy-5-chlorobenzamido>-ethyl)-benzenesulphonyl]-iminodithiocarbonic acid dimethyl ester which melted at 94—96°C were obtained.

c) N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl]-N' - (Δ 2 - cyclohexenyl) - isothio - urea methyl ether. 4.73 g of the ester obtained according to b) were dissolved in 100 ml of dioxane. 1 g of Δ 2-cyclohexenylamine was added thereto and the whole was heated on the steam bath for 1½ hours. After pouring into water and acidification with hydrochloric acid the isothio-urea methyl ether indicated above was obtained as a smeary substance.

d) N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl]-N' - (Δ 2 - cyclohexenyl) - urea. The smeary substance obtained according to c) was dissolved in dioxane, a 2-normal sodium hydroxide solution was added thereto and the solution was heated for 1 hour on the steam bath. After pouring into water and acidification with acetic acid N-[4-(β -<2-methoxy-5-chlorobenzamido>-ethyl)-benzenesulphonyl]-N'-(Δ 2-cyclohexenyl)-urea was obtained as a crystalline precipitate. The substance melted after recrystallization from methanol at 168—169°C.

EXAMPLE 18

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

a) 4.9 g of 1-(Δ 2-cyclohexenyl)-parabanic acid (m.p. 179—181°C) and 2.5 g of triethylamine were dissolved in 200 ml of benzene and 8.9 g of 4-(β -<2-methoxy-5-chlorobenzamido>-ethyl)-benzenesulphochloride (m.p. 102—103°C) were added thereto. The mixture was refluxed for 3 hours and the triethylamine hydrochloride formed was separated while hot by suction-filtration. Petroleum ether fraction, boiling point 40°C to 70°C, was added to the filtrate which had cooled and the crystals which precipitated after a short time were suction-filtered. After the crystals had been recrystallized two times from a mixture of methanol and dimethylformamide, the pure 1 - [4 - (β - <2 - methoxy - 5 - chlorobenzamido>-ethyl) - benzenesulphonyl] - 3' - (Δ 2 - cyclohexenyl) - parabanic acid, melting point 194—196°C. was obtained.

b) 0.5 g of the substance obtained according to a) was heated with 5 ml of dioxane and 10 ml of 1-normal sodium hydroxide solution for 45 minutes on the steam bath. Water was then added thereto, the mixture was acidified and the precipitate obtained was recrystallized from methanol. The melting point of the N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl]-N' - (Δ 2 - cyclohexenyl) - urea so obtained was 168—170°C.

EXAMPLE 19

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

a) 3 g of N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - N' - (Δ 2 - cyclohexenyl) - thiourea (prepared from N-[4-(β -<2-methoxy-5-chlorobenzamido>-ethyl)-benzenesulphonyl]-N'-phenyl-thiourea and Δ 2-cyclohexenylamine, m.p. 152—154°C) were suspended in 50 ml of 2-normal sodium hydroxide solution. Subsequently 10 ml of 35%-hydrogen peroxide were added thereto and the whole was heated for 30 minutes on the steam bath, acidified with dilute hydrochloric acid, the crystalline precipitate was suction-filtered and recrystallized from methanol. The isolated N-[4-(β -<2-methoxy-5-chlorobenzamido>-ethyl)-benzenesulphonyl]-N'-(Δ 2-cyclohexenyl)-urea melted, after recrystallization from methanol, at 168—170°C.

The same compound was obtained when the thiourea mentioned above was desulphurized by treating it 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 2-normal sodium hydroxide solution. 0.22 g of mercury oxide was added thereto and the whole was stirred for 4 hours at 40°C. The mercury sulphide which had formed was suction-filtered, the filtrate was acidified and the precipitate of N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - N' - (Δ 2-

cyclohexenyl) - urea obtained was suction-filtered and recrystallized from methanol. Melting point 168—170°C.

b) 0.52 g of N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - N' - (Δ2 - cyclohexenyl) - thiourea was dissolved in 50 ml of methanol. While stirring 0.22 g of mercury oxide and a small amount of K₂CO₃ were added thereto and the whole was heated to 50—54°C for 3 hours while stirring was continued. After filtration of the mercury sulphide formed, the solution was concentrated and N-[4-(β-<2-methoxy-5-chlorobenzamido>-ethyl)-benzenesulphonyl] - N' - (Δ2-cyclohexenyl) - isourea methyl ether was obtained as a viscous resin. A sample of the above-mentioned isourea ether was covered with concentrated hydrochloric acid in a test tube and while stirring it was heated for several minutes on the steam bath. The crystals of N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - N' - (Δ2 - cyclohexenyl) - urea obtained were recrystallized from methanol, m.p. 166—168°C.

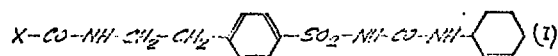
EXAMPLE 20

N-[4-(β-<2-methoxy-5-chlorobenzamido>-ethyl)-benzenesulphonyl]-N'-(Δ2-cyclohexenyl)-urea

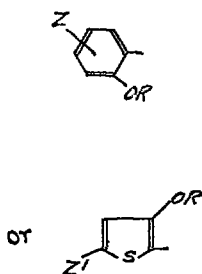
3.2 g of N - [4 - (β - aminoethyl) - benzenesulphonyl] - N' - (Δ2 - cyclohexenyl)-urea (m.p. 185—187°C. prepared by saponification of N-[4-(β-acetamido-ethyl)-benzenesulphonyl]-N'-(Δ2-cyclohexenyl)-urea with sodium hydroxide solution) were suspended in 25 ml of chloroform. After an addition of 1.6 g of pyridine 2.1 g of 2-methoxy-5-chlorobenzoic acid chloride were introduced and while stirring the whole was heated to 40°C for 6 hours. The solution obtained was concentrated *in vacuo* and the smeary residue was extracted with 1%-ammonia. After acidification of the alkaline solution and recrystallization from methanol N-[4-(β-<2-methoxy-5-chlorobenzamido>-ethyl)-benzenesulphonyl]-N'-(Δ2-cyclohexenyl)-urea, melting point 168—170°C, was obtained.

WHAT WE CLAIM IS:—

1. Acylaminoalkyl-benzenesulphonyl-ureas of the general formula



wherein X represents



in which R stands for an alkyl radical containing 1 to 4 carbon atoms,

Z stands for a halogen atom or an alkyl or an alkoxy radical both containing 1 to 4 carbon atoms, and

Z' stands for a halogen atom or an alkyl radical containing 1 to 4 carbon atoms.

2. N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - N' - (Δ2 - cyclohexenyl) - urea.

3. N - [4 - (β - <2 - methoxy - 5 - methylbenzamido> - ethyl) - benzenesulphonyl] - N' - (Δ2 - cyclohexenyl) - urea.

4. Any one of the acylaminoalkyl-benzenesulphonyl-ureas of the general formula given in claim 1 which is described in the Examples herein, other than the compounds claimed in Claims 2 and 3.

cyclohexenyl) - urea obtained was suction-filtered and recrystallized from methanol. Melting point 168—170°C.

b) 0.52 g of N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - N' - (Δ2 - cyclohexenyl) - thiourea was dissolved in 50 ml of methanol. While stirring 0.22 g of mercury oxide and a small amount of K₂CO₃ were added thereto and the whole was heated to 50—54°C for 3 hours while stirring was continued. After filtration of the mercury sulphide formed, the solution was concentrated and N-[4-(β-<2-methoxy-5-chlorobenzamido>-ethyl)-benzenesulphonyl] - N' - (Δ2-cyclohexenyl) - isourea methyl ether was obtained as a viscous resin. A sample of the above-mentioned isourea ether was covered with concentrated hydrochloric acid in a test tube and while stirring it was heated for several minutes on the steam bath. The crystals of N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - N' - (Δ2 - cyclohexenyl) - urea obtained were recrystallized from methanol, m.p. 166—168°C.

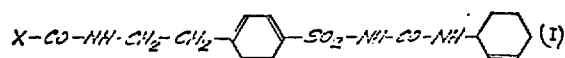
EXAMPLE 20

N-[4-(β-<2-methoxy-5-chlorobenzamido>-ethyl)-benzenesulphonyl]-N'-(Δ2-cyclohexenyl)-urea

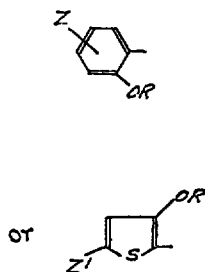
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WHAT WE CLAIM IS:—

1. Acylaminoalkyl-benzenesulphonyl-ureas of the general formula



wherein X represents



in which R stands for an alkyl radical containing 1 to 4 carbon atoms, Z stands for a halogen atom or an alkyl or an alkoxy radical both containing 1 to 4 carbon atoms, and

Z' stands for a halogen atom or an alkyl radical containing 1 to 4 carbon atoms.

2. N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - N' - (Δ2 - cyclohexenyl) - urea.

3. N - [4 - (β - <2 - methoxy - 5 - methylbenzamido> - ethyl) - benzenesulphonyl] - N' - (Δ2 - cyclohexenyl) - urea.

4. Any one of the acylaminoalkyl-benzenesulphonyl-ureas of the general formula given in claim 1 which is described in the Examples herein, other than the compounds claimed in Claims 2 and 3.



5. Physiologically tolerable salts of any one of the compounds claimed in any one of claims 1 to 4.

6. A process for the manufacture of acylaminoalkylbenzenesulphonyl-ureas as claimed in any one of claims 1 to 5, conducted substantially as hereinbefore described.

5 7. 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 5, in admixture or conjunction with a pharmaceutically suitable carrier. 5

10 8. A pharmaceutical preparation as claimed in claim 7, which is in the form of a tablet. 10

9. A pharmaceutical preparation as claimed in claim 7, or claim 8, which contains in dosage unit form from 0.5 to 100 mg of the active ingredient.

10. A pharmaceutical preparation as claimed in claim 9, which contains in dosage unit form from 2 to 10 mg of the active ingredient.

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