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PATENT SPECIFICATION

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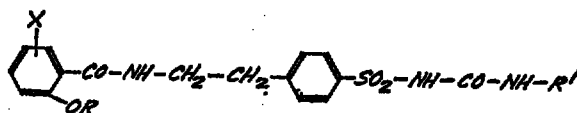
COMPLETE SPECIFICATION

Benzenesulphonyl-Ureas and Process for their manufacture

We, **FARBWERKE HOECHST AKTIENGESSELLSCHAFT**, vormals Meister Lucius & Brüning, a Body Corporate recognised under German Law, of 6230 Frankfurt (M)-Hoechst, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

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

The present invention provides benzenesulphonyl-ureas of the general formula



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

In the above formula

R represents a lower alkyl group, preferably a methyl group, or a lower alkenyl group,

X represents a halogen atom, preferably a chlorine atom, a lower alkyl group, preferably a methyl group, or a lower alkoxy group, preferably a methoxy group, and

R¹ represents a cyclohexyl, methylcyclohexyl or ethylcyclohexyl group, the methyl or ethyl group being preferably in the 4-position of the cyclohexyl group, or an endomethylene-cyclohexenylmethyl or endomethylene-cyclohexylmethyl group. The substituent represented by X is in the 4-position or, preferably, in the 5-position to the carbonamide group.

The term "lower" in qualifying alkyl, alkoxy and alkenyl groups is used throughout this Specification to mean alkyl, alkoxy and alkenyl groups containing 1 to 4 carbon atoms in a straight or branched chain.

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

R¹ may represent, for example, cyclohexyl, 4-methyl-cyclohexyl (preferably in the trans form), 4-ethyl-cyclohexyl, 2,5-endomethylene-cyclohexenylmethyl or 2,5-endomethylene-cyclohexylmethyl.

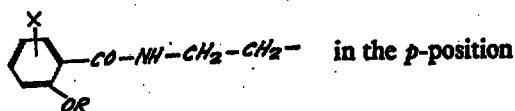
The benzenesulphonyl-ureas of the present invention can be prepared by methods which are generally used for the preparation of compounds of this class. Accordingly, the present invention also provides a process for the manufacture of the new compounds, which comprises

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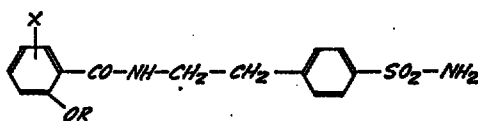
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(a) reacting benzenesulphonyl isocyanates, benzenesulphonyl carbamic acid esters, benzenesulphonyl thiocarbamic acid esters, benzenesulphonyl carbamic acid halides or benzenesulphonyl-ureas carrying the substituent



5 with R¹-substituted amines or their salts; or

(b) reacting benzenesulphonamides of the formula



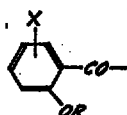
or their salts with R¹-substituted isocyanates, carbamic acid esters, thiocarbamic acid esters, carbamic acid halides or ureas; or

10 (c) reacting correspondingly substituted benzenesulphonyl-halides with R¹-substituted ureas, isourea ethers, isothiurea ethers or parabanic acids and hydrolysing the benzenesulphonyl-isourea ethers, benzenesulphonyl-isothiurea ethers or benzenesulphonyl parabanic acids obtained in this way or by another method; or

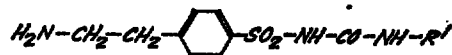
15 (d) replacing in a known manner the sulphur atom in correspondingly substituted benzenesulphonyl-thioureas by an oxygen atom; or

(e) oxidizing correspondingly substituted benzenesulphinyl-ureas or benzenesulphenyl-ureas; or

(f) introducing by acylation the radical



20 in one or several steps into benzenesulphonyl-ureas of the formula



and, if desired, converting the reaction products so obtained into salts by treatment with a base, for example an alkaline agent.

25 When a mixture of the *cis* and *trans* isomers of 4-methyl (or ethyl)-cyclohexylamine or of a derivative thereof is used as starting material, then the end product contains a mixture of the *cis* and *trans* isomers.

Instead of benzenesulphonyl isocyanates, there may also be used reaction products of benzenesulphonyl isocyanates with acid amides such as caprolactam or butyrolactam, or further with weakly basic amines such as carbazoles.

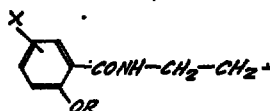
30 The benzenesulphonyl-carbamic acid esters or benzenesulphonyl-thiocarbamic acid esters may carry in the alcohol component a low molecular weight alkyl group or a phenyl group. The same applies to the R¹-substituted carbamic acid esters or the corresponding monothiocarbamic acid esters. By a low molecular weight or lower

alkyl group, there is to be understood herein an alkyl group containing no more than 4 carbon atoms.

As carbamic acid halides, the chlorides are advantageously used.

The benzenesulphonyl-ureas used as starting materials in the process of the present invention may be unsubstituted at the side of the urea molecule opposite to the sulphonyl group or may be mono- or di-substituted, preferably by low molecular weight alkyl or aryl groups; instead of benzenesulphonyl-ureas substituted in such a manner, there may also be used corresponding N-benzenesulphonyl-N'-acyl-ureas (acyl representing a low molecular weight aliphatic acyl group such as acetyl, propionyl or butyryl, but also a benzoyl group), and, in addition, bis-(benzenesulphonyl)-ureas. Such bis-(benzenesulphonyl)-ureas of N-benzenesulphonyl-N'-acyl-ureas may be treated, for example, with amines of the formula R^1NH_2 and the salts obtained may be heated to elevated temperatures, in particular to temperatures above $100^\circ C$.

It is also possible to start from ureas of the formula $R^1-NH-CO-NH_2$ or from acylated ureas of the formula $R^1-NH-CO-NH-acyl$, in which acyl preferably represents a low molecular weight aliphatic or aromatic acid group or a nitro group, or from phenyl-ureas of the formula $R^1-NH-CO-NH-C_6H_5$, or from diphenyl-ureas of the formula $R^1-NH-CO-N(C_6H_5)_2$, in which the phenyl groups 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 $-S-$, or from N,N'-disubstituted ureas of the formula $R^1-NH-CO-NH-R^1$ and to react these compounds with



substituted benzenesulphonamides.

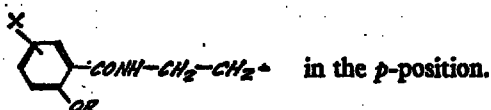
In the correspondingly substituted benzenesulphonyl-thioureas, the sulphur atom can be replaced by an oxygen atom, for example, with the aid of oxides or salts of heavy metals or with the use of oxidizing agents such as, for example, as hydrogen peroxide, sodium peroxide or nitrous acid.

The thioureas can likewise be desulphurized by treatment with phosgene or phosphorus pentachloride. Chloroformic acid amidines or chloroformic acid carbodiimides obtained as intermediates can be converted into the benzenesulphonyl-ureas by an appropriate treatment, for example, by hydrolysis or the addition of water.

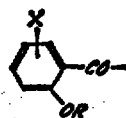
The corresponding isothiurea ethers behave in a manner analogous to the thioureas, and can, therefore, be used as equivalent starting materials for the desulphurizing reactions.

With regard to the reaction condition, the manner of carrying out the process of the present invention 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, at room temperature or at an elevated temperature.

As starting materials, there may be used compounds which contain a benzene radical which is substituted by the group



Examples of the component



of the formula indicated above are:



60

Thus, it has been found, for example, that 10 mg/kg of body weight of N - [4 - (β - <2 - methoxy - 5 - methyl - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea and 10 mg/kg of body weight of N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans) provoke after 3 hours a lowering of the blood sugar of 9% and 15%, respectively, after 24 hours a lowering of 24% and 27%, respectively, and after 48 hours a lowering of 12% and 19%, respectively.

In the same manner, it has been found that 10 mg/kg of body weight of N - [4 - (β - <2 - methoxy - 5 - methyl - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans) and 10 mg/kg of body weight of N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea provoke after 3 hours a lowering of the blood sugar of 37% and 19%, respectively, after 24 hours a lowering of 25% and 23%, respectively, after 48 hours a lowering of 28% and 23%, respectively, and even after 72 hours a lowering of 19% and 13%, respectively, whereas the hitherto known N - (4 - methyl - benzenesulphonyl) - N' - butyl - urea has no blood sugar lowering effect when fed to rabbits in a dose of less than 25 mg/kg of body weight.

The strong hypoglycemic action of the benzenesulphonyl-ureas of the present invention becomes more evident when the dose is further reduced. When N - [4 - (β - <2 - methoxy - 5 - methyl - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea is administered to a rabbit in a dose of 0.005 mg/kg of body weight, or N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea is administered in a dose of 0.02 mg/kg of body weight, or N - [4 - (β - <2 - methoxy - 5 - methyl - benzamido> - ethyl) - benzenesulphonyl] - (4 - methyl - cyclohexyl) - urea is administered in a dose of 0.02 mg/kg of body weight, or N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea is administered in a dose of 0.02 mg/kg of body weight, a distinct lowering of the blood sugar can still be observed in rabbits.

The present invention further provides pharmaceutical preparations which comprise the new benzenesulphonyl-ureas or physiologically tolerable salts thereof, in admixture or conjunction with a pharmaceutically suitable carrier.

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

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

A pharmaceutical preparation containing one of the new benzenesulphonyl-ureas or physiologically tolerable salts as active substance, for example a tablet or a powder, with or without the aforesaid carriers is advantageously brought into a suitable unit dosage form. The dose chosen should comply with the activity of the benzenesulphonyl-urea or physiologically tolerable salt thereof used and the desired effect. Advantageously, the dosage per unit amounts to about 0.5 to 100 milligrams, preferably 2 to 10 milligrams, 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

N-[4-(β -<2,5-dimethoxy-benzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea

9.1 Grams of 4 - (β - <2,5 - dimethoxy - benzamido> - ethyl) - benzene - sulphonamide (melting point 193—194°C) were dissolved in 12.5 millilitres of 2N sodium hydroxide solution and 30 millilitres of acetone; to this solution were added dropwise, at 0—5°C, 3.3 grams of cyclohexyl isocyanate. The whole was stirred for 3 hours, diluted with water and methanol, undissolved matter was separated by filtration and the filtrate was acidified with dilute hydrochloric acid. The N - [4 - (β - <2,5 - dimethoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl -



urea which precipitated in the form of crystals melted after recrystallization from methanol at 143—145°C.

In an analogous manner, there were obtained:

- | | | | |
|----|---|----|----|
| 5 | N - [4 - (β - <2,5 - dimethoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 155—156°C (from methanol); | 5 | 5 |
| | from 4 - (β - <2 - methoxy - 5 - ethoxy - benzamido> - ethyl) - benzene - sulphonamide, melting point 190—191°C; | | |
| 10 | N - [4 - (β - <2 - methoxy - 5 - ethoxy - benzamido> - ethyl) - benzene - sulphonyl] - N' - cyclohexyl - urea, melting point 146—148°C (from methanol), | 10 | 10 |
| | N - [4 - (β - <2 - methoxy - 5 - ethoxy - benzamido> - ethyl) - benzene - sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 130—132°C (from methanol), and | | |
| 15 | N - [4 - (β - <2 - methoxy - 5 - ethoxy - benzamido> - ethyl) - benzene - sulphonyl] - N' - (4 - ethyl - cyclohexyl) - urea (trans), melting point 108—110°C (with decomposition) (from methanol); | 15 | 15 |
| | from 4 - (β - <2,4 - dimethoxy - benzamido> - ethyl) - benzenesulphonamide, melting point 200—202°C; | | |
| 20 | N - [4 - (β - <2,4 - dimethoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea, melting point 193—194°C (from methanol), and | 20 | 20 |
| | N - [4 - (β - <2,4 - dimethoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 208—210°C (from methanol/dimethylformamide); | | |
| 25 | from 4 - (β - <2 - methoxy - 4 - ethoxy - benzamido> - ethyl) - benzene - sulphonamide (melting point 183—185°C); | 25 | 25 |
| | N - [4 - (β - <2 - methoxy - 4 - ethoxy - benzamido> - ethyl) - benzene - sulphonyl] - N' - cyclohexyl - urea, melting point 172—174°C (from methanol); | | |
| 30 | from 4 - (β - <2 - methoxy - 5 - fluoro - benzamido> - ethyl) - benzene - sulphonamide, melting point 167—169°C; | 30 | 30 |
| | N - [4 - (β - <2 - methoxy - 5 - fluoro - benzamido> - benzenesulphonyl] - N' - cyclohexyl - urea, melting point 176—178°C (from methanol), | | |
| 35 | N - [4 - (β - <2 - methoxy - 5 - fluoro - benzamido> - ethyl) - benzene - sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 185—187°C (from methanol/dimethylformamide), and | 35 | 35 |
| | N - [4 - (β - <2 - methoxy - 5 - fluoro - benzamido> - ethyl) - benzene - sulphonyl] - N' - (4 - ethyl - cyclohexyl) - urea (trans), melting point 179—180°C (from methanol/dimethylformamide); | | |
| 40 | from 4 - (β - <2 - methoxy - 5 - bromo - benzamido> - ethyl) - benzene - sulphonamide, melting point 223—224°C; | 40 | 40 |
| | N - [4 - (β - <2 - methoxy - 5 - bromo - benzamido> - ethyl) - benzene - sulphonyl] - N' - cyclohexyl - urea, melting point 161—163°C (from methanol), and | | |
| 45 | N - [4 - (β - <2 - methoxy - 5 - bromo - benzamido> - ethyl) - benzene - sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 187—189°C (from methanol); | 45 | 45 |
| | from 4 - (β - <2 - ethoxy - 5 - chloro - benzamido> - ethyl) - benzene - sulphonamide, melting point 168—170°C; | | |
| 50 | N - [4 - (β - <2 - ethoxy - 5 - chloro - benzamido> - ethyl) - benzene - sulphonyl] - N' - cyclohexyl - urea, melting point 171—173°C (from methanol), | 50 | 50 |
| | N - [4 - (β - <2 - ethoxy - 5 - chloro - benzamido> - ethyl) - benzene - sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 156—158°C (from methanol), and | | |
| 55 | N - [4 - (β - <2 - ethoxy - 5 - chloro - benzamido> - ethyl) - benzene - sulphonyl] - N' - (4 - ethyl - cyclohexyl) - urea (trans), melting point 135—137°C (from methanol); | 55 | 55 |
| | from 4 - (β - <2 - n - propoxy - 5 - chloro - benzamido> - ethyl) - benzene - sulphonamide (melting point 192—194°C); | | |
| 60 | N - [4 - (β - <2 - n - propoxy - 5 - chloro - benzamido> - ethyl) - benzene - sulphonyl] - N' - cyclohexyl - urea, melting point 166—168°C (from methanol), and | 60 | 60 |
| | N - [4 - (β - <2 - n - propoxy - 5 - chloro - benzamido> - ethyl) - benzene - sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans) melting point 160—161°C (from methanol); | | |
| 65 | from 4 - (β - <2 - allyloxy - 5 - chloro - benzamido> - ethyl) - benzene - sulphonamide, melting point 183—184°C; | 65 | 65 |

N - [4 - (β - $\langle$ 2 - allyloxy - 5 - chloro - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - cyclohexyl - urea, melting point 155—157°C (from methanol),

N - [4 - (β - $\langle$ 2 - allyloxy - 5 - chloro - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 159—161°C (from methanol), and

N - [4 - (β - $\langle$ 2 - allyloxy - 5 - chloro - benzamido $\rangle$ - ethyl) - benzenesulphonyl] - N' - (4 - ethyl - cyclohexyl) - urea (trans), melting point 162—164°C (from methanol);

from 4 - (β - $\langle$ 2 - methoxy - 4 - chloro - benzamido $\rangle$ - ethyl) - benzene - sulphonamide, melting point 187—188°C:

N - [4 - (β - $\langle$ 2 - methoxy - 4 - chloro - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - cyclohexyl - urea, melting point 200—201°C (from methanol/dimethylformamide),

N - [4 - (β - $\langle$ 2 - methoxy - 4 - chloro - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 204—205°C (from methanol/dimethylformamide), and

N - [4 - (β - $\langle$ 2 - methoxy - 4 - chloro - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - (4 - ethyl - cyclohexyl) - urea (trans), melting point 184—186°C (from methanol/dimethylformamide);

from 4 - (β - $\langle$ 2 - ethoxy - 5 - methyl - benzamido $\rangle$ - ethyl) - benzene - sulphonamide, melting point 147—148°C:

N - [4 - (β - $\langle$ 2 - ethoxy - 5 - methyl - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - cyclohexyl - urea, melting point 159—161°C (from methanol), and

N - [4 - (β - $\langle$ 2 - ethoxy - 5 - methyl - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea, melting point 181—182°C (from methanol/dimethylformamide);

from 4 - (β - $\langle$ 2 - allyloxy - 5 - methyl - benzamido $\rangle$ - ethyl) - benzene - sulphonamide, melting point 140—141°C:

N - [4 - (β - $\langle$ 2 - allyloxy - 5 - methyl - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - cyclohexyl - urea, melting point 156—158°C (from methanol), and

N - [4 - (β - $\langle$ 2 - allyloxy - 5 - methyl - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea, melting point 143—145°C (from methanol);

from 4 - (β - $\langle$ 2 - methoxy - 4 - methyl - benzamido $\rangle$ - ethyl) - benzene - sulphonamide, melting point 188—189°C:

N - [4 - (β - $\langle$ 2 - methoxy - 4 - methyl - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - cyclohexyl - urea, melting point 209—211°C (from methanol/dimethylformamide),

N - [4 - (β - $\langle$ 2 - methoxy - 4 - methyl - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 208—209°C (from methanol/dimethylformamide), and

N - [4 - (β - $\langle$ 2 - methoxy - 4 - methyl - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - (4 - ethyl - cyclohexyl) - urea (trans), melting point 168—169°C (from methanol);

from 4 - (β - $\langle$ 2 - methoxy - 5 - chloro - benzamido $\rangle$ - ethyl) - benzene - sulphonamide, melting point: 214—216°C:

N - [4 - (β - $\langle$ 2 - methoxy - 5 - chloro - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - (3 - methyl - cyclohexyl) - urea, melting point 181—183°C (from methanol), and

N - [4 - (β - $\langle$ 2 - methoxy - 5 - chloro - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - (2 - methyl - cyclohexyl) - urea, melting point 164—166°C (from methanol);

from 4 - (β - $\langle$ 2 - methoxy - 4 - chloro - benzamido $\rangle$ - ethyl) - benzene - sulphonamide, melting point 185—186°C:

N - [4 - (β - $\langle$ 2 - methoxy - 4 - chloro - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - (2,5 - endomethylene - cyclohexylmethyl) - urea, melting point 182—184°C (from methanol);

from 4 - (β - $\langle$ 2 - methoxy - 5 - bromo - benzamido $\rangle$ - ethyl) - benzene - sulphonamide, melting point 224—225°C:

N - [4 - (β - $\langle$ 2 - methoxy - 5 - bromo - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - (4 - ethyl - cyclohexyl) - urea (trans), melting point 186—188°C (from methanol);

	from 4 - (β - $\langle$ 2 - ethoxy - 5 - methyl - benzamido $\rangle$ - ethyl) - benzene - sulphonamide, melting point 147—148°C:	
5	N - [4 - (β - $\langle$ 2 - ethoxy - 5 - methyl - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - (4 - ethyl - cyclohexyl) - urea (trans), melting point 179—181°C (from methanol);	5
	from 4 - (β - $\langle$ 2 - <i>n</i> - propoxy - 5 - methyl - benzamido $\rangle$ - ethyl) - benzene - sulphonamide, melting point 166—167°C:	
10	N - [4 - (β - $\langle$ 2 - <i>n</i> - propoxy - 5 - methyl - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - cyclohexyl - urea, melting point 135—137°C (from methanol), and	10
	N - [4 - (β - $\langle$ 2 - <i>n</i> - propoxy - 5 - methyl - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 146—147°C (from methanol);	15
15	from 4 - (β - $\langle$ 2 - ethoxy - 4 - chloro - benzamido $\rangle$ - ethyl) - benzene - sulphonamide, melting point 177—178°C:	15
	N - [4 - (β - $\langle$ 2 - ethoxy - 4 - chloro - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - cyclohexyl - urea, melting point 184—185°C (from methanol), and	20
20	N - [4 - (β - $\langle$ 2 - ethoxy - 4 - chloro - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 196—197°C (from methanol);	20
	from 4 - (β - $\langle$ 2 - ethoxy - 5 - bromo - benzamido $\rangle$ - ethyl) - benzenesulphonamide, melting point 182—183°C:	25
25	N - [4 - (β - $\langle$ 2 - ethoxy - 5 - bromo - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - cyclohexyl - urea, melting point 166—168°C (from methanol),	25
	N - [4 - (β - $\langle$ 2 - ethoxy - 5 - bromo - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 153—155°C (from methanol), and	30
30	N - [4 - (β - $\langle$ 2 - ethoxy - 5 - bromo - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - (4 - ethyl - cyclohexyl) - urea (trans), melting point 167—169°C (from methanol);	30
	from 4 - (β - $\langle$ 2 - <i>n</i> - butoxy - 5 - methyl - benzamido $\rangle$ - ethyl) - benzene - sulphonamide, melting point 149—151°C:	35
35	N - [4 - (β - $\langle$ 2 - <i>n</i> - butoxy - 5 - methyl - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - cyclohexyl - urea, melting point 151—152°C (from methanol), and	35
	N - [4 - (β - $\langle$ 2 - <i>n</i> - butoxy - 5 - methyl - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 173—174°C (from methanol);	40
40	from 4 - (β - $\langle$ 2 - ethoxy - 5 - fluoro - benzamido $\rangle$ - ethyl) - benzene - sulphonamide, melting point 171—173°C:	40
	N - [4 - (β - $\langle$ 2 - ethoxy - 5 - fluoro - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - cyclohexyl - urea, melting point 134—136°C (from methanol),	45
45	N - [4 - (β - $\langle$ 2 - ethoxy - 5 - fluoro - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea, melting point 149—151°C (from methanol), and	45
	N - [4 - (β - $\langle$ 2 - ethoxy - 5 - fluoro - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - (4 - ethyl - cyclohexyl) - urea, melting point 165—167°C (from methanol);	50
50	from 4 - (β - $\langle$ 2 - <i>n</i> - propoxy - 5 - fluoro - benzamido $\rangle$ - ethyl) - benzene - sulphonamide, melting point 180—182°C:	50
	N - [4 - (β - $\langle$ 2 - <i>n</i> - propoxy - 5 - fluoro - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - cyclohexyl - urea, melting point 165—167°C (from methanol), and	55
55	N - [4 - (β - $\langle$ 2 - <i>n</i> - propoxy - 5 - fluoro - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 181—182°C (from methanol);	55
	from 4 - (β - $\langle$ 2 - methoxy - 5 - ethyl - benzamido $\rangle$ - ethyl) - benzene - sulphonamide, melting point 193—195°C:	60
60	N - [4 - (β - $\langle$ 2 - methoxy - 5 - ethyl - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - cyclohexyl - urea, melting point 160—162°C (from methanol),	60
	N - [4 - (β - $\langle$ 2 - methoxy - 5 - ethyl - benzamido $\rangle$ - ethyl) - benzene - sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 180—181°C (from methanol), and	65
65	N - [4 - (β - $\langle$ 2 - methoxy - 5 - ethyl - benzamido $\rangle$ - ethyl) - benzene -	65

- 6 sulphonyl] - N' - (4 - ethyl - cyclohexyl) - urea (trans), melting point 110—112°C (from methanol);
from 4 - (β - <2 - methoxy - 5 - tert. butyl - benzamido> - ethyl) - benzene -
5 sulphonamide, melting point 166—167°C;
5 N - [4 - (β - <2 - methoxy - 5 - tert. butyl - benzamido> - ethyl) - benzene -
1 N' - sulphonyl] - cyclohexyl - urea, melting point 136—138°C (from methanol), and
10 N - [4 - (β - <2 - methoxy - 5 - tert. butyl - benzamido> - ethyl) -
benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point:
120—122°C (from methanol);
10 from 4 - (β - <2 - methoxy - 5 - isopropyl - benzamido> - ethyl) - benzene -
sulphonamide, melting point 192—194°C;
10 N - [4 - (β - <2 - methoxy - 5 - isopropyl - benzamido> - ethyl) - benzene -
sulphonyl] - N' - cyclohexyl - urea, melting point 116—118°C (from methanol),
and
15 N - [4 - (β - 2 - methoxy - 5 - isopropyl - benzamido - ethyl) - benzene -
15 sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 188—
189°C (from methanol);
from 4 - (β - <2 - ethoxy - 5 - ethyl - benzamido> - ethyl) - benzene -
20 sulphonamide, melting point 139—141°C;
20 N - [4 - (β - <2 - ethoxy - 5 - ethyl - benzamido> - ethyl) - benzene -
sulphonyl] - N' - cyclohexyl - urea, melting point 149—152°C (from methanol),
20 N - [4 - (β - <2 - ethoxy - 5 - ethyl - benzamido> - ethyl) - benzene -
sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 171—
173°C (from methanol), and
25 N - [4 - (β - <2 - ethoxy - 5 - ethyl - benzamido> - ethyl) - benzene -
25 sulphonyl] - N' - (4 - ethyl - cyclohexyl) - urea (trans), melting point 153—
155°C (from methanol);
from 4 - (β - <2 - methoxy - 4 - bromo - benzamido> - ethyl) - benzene -
30 sulphonamide, melting point 202—203°C;
30 N - [4 - (β - <2 - methoxy - 4 - bromo - benzamido> - ethyl) - benzene -
sulphonyl] - N' - cyclohexyl - urea, melting point 201—203°C (from methanol/
dimethylformamide), and
35 N - [4 - (β - <2 - methoxy - 4 - bromo - benzamido> - ethyl) - benzene -
35 sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 205—
206°C (from methanol/dimethylformamide);
from 4 - (β - <2 - methoxy - 5 - iodo - benzamido> - ethyl) - benzene -
35 sulphonamide, melting point 236—237°C;
40 N - [4 - (β - <2 - methoxy - 5 - iodo - benzamido> - ethyl) - benzene -
40 sulphonyl] - N' - cyclohexyl - urea, melting point 169—170°C (from methanol),
and
40 N - [4 - (β - <2 - methoxy - 5 - iodo - benzamido> - ethyl) - benzene -
40 sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 141—
143°C (from methanol);
45 from 4 - (β - <2 - allyloxy - 5 - fluoro - benzamido> - ethyl) - benzene -
45 sulphonamide, melting point 160—162°C;
45 N - [4 - (β - <2 - allyloxy - 5 - fluoro - benzamido> - ethyl) - benzene -
45 sulphonyl] - N' - cyclohexyl - urea, melting point 153—155°C (from methanol),
and
50 N - [4 - (β - <2 - allyloxy - 5 - fluoro - benzamido> - ethyl) - benzene -
50 sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 152—154°C
(from methanol).

EXAMPLE 2

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

55 7 Grams of N - [4 - (β - <2 - methoxy - 5 - methyl - benzamido> - ethyl) -
benzenesulphonyl] - methyl - urethane (melting point 175—177°C) were suspended
in 200 millilitres of xylene and combined at 80°C with 1.9 grams of cyclohexylamine.
After a short time, the temperature of the surrounding oil bath was raised to
150°C and held for 30 minutes at this temperature. During that time the reaction mix-
60 ture dissolved and the methanol separated by distillation. Upon cooling, N - [4 -
(β - <2 - methoxy - 5 - methyl - benzamido> - ethyl) - benzenesulphonyl] -
N' - cyclohexyl - urea precipitated in the form of crystals; after recrystallization
from methanol/dimethylformamide, the compound melted at 187—188°C.

In an analogous manner there were obtained:

N - [4 - (β - $\leq$ 2 - methoxy - 5 - methyl - benzamido) - ethyl) - benzene - sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 157—159°C (from methanol),

N - [4 - (β - $\leq$ 2 - methoxy - 5 - methyl - benzamido) - ethyl) - benzene - sulphonyl] - N' - (3 - methyl - cyclohexyl) - urea, melting point 176—178°C (from methanol/dimethylformamide), and

N - [4 - (β - $\leq$ 2 - methoxy - 5 - methyl - benzamido) - ethyl) - benzene - sulphonyl] - N' - (4 - ethyl - cyclohexyl) - urea, melting point 164—166°C (from methanol).

EXAMPLE 3

N-[4-(β - $\leq$ 2-methoxy-5-chloro-benzamido)-ethyl]-benzenesulphonyl]-N'-cyclohexyl-urea

A mixture of 10.3 grams of N - [4 - (β - $\leq$ 2 - methoxy - 5 - chloro - benz - amido) - ethyl) - benzenesulphonyl] - urea (melting point 171—173°C), 300 millilitres of toluene, 30 millilitres of glycol monomethyl ether, 1.65 grams of glacial acetic acid and 2.8 grams of cyclohexylamine was heated for 5 hours under reflux. The mixture was then concentrated under reduced pressure and the residue was treated with alcohol. The N - [4 - (β - $\leq$ 2 - methoxy - 5 - chloro - benzamido) - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea obtained as crude product was filtered off with suction and recrystallized from methanol. Melting point 169—170°C.

In an analogous manner there were obtained:

N - [4 - (β - $\leq$ 2 - methoxy - 5 - chloro - benzamido) - ethyl) - benzene - sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 189—190°C (from methanol),

N - [4 - (β - $\leq$ 2 - methoxy - 5 - chloro - benzamido) - ethyl) - benzene - sulphonyl] - N' - (4 - ethyl - cyclohexyl) - urea (trans), melting point 184—185°C (from methanol), and

N - [4 - (β - $\leq$ 2 - methoxy - 5 - chloro - benzamido) - ethyl) - benzene - sulphonyl] - N' - (2,5 - endomethylene - Δ^3 - cyclohexenylmethyl) - urea melting point 160—162°C (from methanol).

EXAMPLE 4

N-[4-(β - $\leq$ 2-methoxy-5-methyl-benzamido)-ethyl]-benzenesulphonyl]-N'-(2,5-endomethylene-cyclohexyl-methyl)-urea

a) 3 Grams of N - [4 - (β - $\leq$ 2 - methoxy - 5 - methyl - benzamido) - ethyl) - benzenesulphonyl] - N' - (2,5 - endomethylene - cyclohexyl - methyl) - thiourea (prepared by the reaction of 4 - (β - $\leq$ 2 - methoxy - 5 - methyl - benz - amido) - ethyl) - benzenesulphonamide with 2,5 - endomethylene - cyclohexyl - methyl - isothiocyanate in boiling acetone in the presence of potassium carbonate, melting point 165—167°C, from methanol/dimethylformamide) were suspended in 50 millilitres of 2N sodium hydroxide solution. 10 Millilitres of 35% hydrogen peroxide were then added. The whole was heated for 30 minutes on a steam bath, acidified with dilute hydrochloric acid, and the crystalline precipitate was filtered off with suction and recrystallized from methanol. The N - [4 - (β - $\leq$ 2 - methoxy - 5 - methyl - benzamido) - ethyl) - benzenesulphonyl] - N' - (2,5 - endomethylene - cyclohexyl - methyl) - urea so obtained melted, after recrystallization from methanol, at 142—144°C. The same compound was obtained by treating the thiourea mentioned at the beginning of this Example with mercury oxide in the presence of sodium hydroxide solution, whereby it was desulphurized. For this purpose, 0.5 gram of the thiourea was dissolved in 10 millilitres of dioxan and 10 millilitres of 2N sodium hydroxide solution. The solution was combined with 0.22 gram of HgO and stirred for 4 hours at 40°C. The mercury sulphide that had formed was separated by filtration with suction, the filtrate was acidified and the precipitate that had separated and that constituted the N - [4 - (β - $\leq$ 2 - methoxy - 5 - methyl - benz - amido) - ethyl) - benzenesulphonyl] - N' - (2,5 - endomethylene - cyclohexyl - methyl) - urea was separated by filtration with suction and recrystallized from methanol. Melting point 142—144°C.

In an analogous manner, there was obtained from N - [4 - (β - $\leq$ 2 - methoxy - 5 - chloro - benzamido) - ethyl) - benzenesulphonyl] - N' - (2,5 - endomethylene - cyclohexyl - methyl) - thiourea (melting point 171—173°C):

N - [4 - (β - $\leq$ 2 - methoxy - 5 - chloro - benzamido) - ethyl) - benzene - sulphonyl] - N' - (2,5 - endomethylene - cyclohexyl - methyl) - urea, melting point 181—183°C (from methanol/dimethylformamide).



b) 0.52 Gram of N - [4 - (β - <2 - methoxy - 5 - methyl - benzamido> - ethyl) - benzenesulphonyl] - N' - (2,5 - endomethylene - cyclohexyl - methyl) - thiourea was dissolved in 50 millilitres of methanol. 0.22 Gram of mercury oxide and a small amount of potassium carbonate were added, while stirring, and the whole was heated for 3 hours at 50—55°C, while the stirring was continued. After separation by filtration of the mercury oxide that had formed, the filtrate was concentrated and the residue constituting N - [4 - (β - <2 - methoxy - 5 - methyl - benzamido> - ethyl) - benzenesulphonyl] - N' - (2,5 - endomethylene - cyclohexyl - methyl) - isourea - methyl ether was recrystallized from dilute methanol. The compound melted at 102—104°C.

Concentrated hydrochloric acid was poured over a sample of the above-mentioned isourea ether in a reaction tube and the whole was heated for some minutes on a steam bath, while stirring. The crystallise of N - [4 - (β - <2 - methoxy - 5 - methyl - benzamido> - ethyl) - benzenesulphonyl] - N' - (2,5 - endomethylene - cyclohexyl - methyl) - urea so obtained was recrystallized from methanol. Melting point 142—144°C.

c) 0.52 Grams of N - [4 - (β - <2 - methoxy - 5 - methyl - benzamido> - ethyl) - benzenesulphonyl] - N' - (2,5 - endomethylene - cyclohexyl - methyl) - thio - urea was dissolved in 50 millilitres of methanol. After the addition of 0.3 gram of methyl iodide, the whole was heated for 2½ hours under reflux at the boil. After concentration a resinous residue constituting N - [4 - (β - <2 - methoxy - 5 - methyl - benzamido> - ethyl) - benzenesulphonyl] - N' - (2,5 - endomethylene - cyclohexyl - methyl) isothiurea methyl ether was obtained which was dissolved in 10 millilitres of dioxan. After the addition of 20 millilitres of 2N sodium hydroxide solution, the solution was heated for 1 hour on a steam bath. By the introduction of water and acidification with hydrochloric acid, N - [4 - (β - <2 - methoxy - 5 - methyl - benzamido> - ethyl) - benzenesulphonyl] - N' - (2,5 - endomethylene - cyclohexyl - methyl) - urea was obtained which melted at 142—144°C, after recrystallization from methanol.

In a manner analogous to that described in Example 4a, there was obtained: from N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - (2,5 - endomethylene - cyclohexylmethyl) - thiourea, prepared from the corresponding sulphonamide and 2,5 - endomethylene - cyclohexyl - methyl - isothiocyanate (melting point: 171—173°C):

N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzene - sulphonyl] - N' - (2,5 - endomethylene - cyclohexyl - methyl) - urea, melting point 181—183°C (from methanol/dimethylformamide).

EXAMPLE 5

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

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

74 Grams of 4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonamide were dissolved in 350 millilitres of dimethylformamide. 23 Grams of carbon disulphide and then a solution of 34 grams of potassium hydroxide in 50 millilitres of water were added dropwise, while stirring. Stirring was continued 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 which had precipitated was filtered off with suction, washed with alcohol and dried. Yield: 60 grams.

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

36 Grams of the potassium salt obtained as described under paragraph (a) were dissolved in 60 millilitres of 1N-sodium hydroxide solution. 12.6 Grams of dimethyl sulphate were added, while shaking, to the clear solution. The mixture heated up. After standing for 30 minutes, a semi-solid oil was separated by decantation. After washing with water, the oil crystallized. The product was recrystallized from dilute methanol; in this manner 30 grams 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' - cyclohexyl - isothiurea methyl ether.

4.73 Grams of the ester obtained as described under paragraph (b) were dissolved in 100 millilitres of dioxan. 1 Gram of cyclohexylamine was added and the whole was heated for 1½ hours on a steam bath. Upon pouring of this mixture into water and acidification with hydrochloric acid, the above-indicated isothiourrea was obtained in the form of an oil.

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

The oil obtained as described under paragraph (c) was dissolved in dioxan, 2N sodium hydroxide solution was added and the solution was heated for 1 hour on a steam bath. After having poured the whole into water and acidified with acetic acid, N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl urea was obtained in the form of a crystalline precipitate. After recrystallization from methanol, the substance melted at 170—172°C.

EXAMPLE 6

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

75 Grams of 4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonamide and 56.3 grams of ground potassium carbonate were suspended in 1.5 litres of acetone and the whole was heated for 3 hours under reflux. 26.5 Grams of cyclohexyl-isocyanate were then added and heating was continued for 5 hours. The precipitate that had formed was filtered off with suction, suspended in water and acidified with dilute hydrochloric acid. After filtration with suction there was obtained N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea which, after recrystallization from methanol, melted at 172—173°C.

EXAMPLE 7

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

a) 4.9 Grams of 1-cyclohexyl-parabanic acid and 2.5 grams of triethylamine were dissolved in 200 millilitres of benzene and combined with 8.9 grams of 4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphochloride (melting point 102—103°C). The mixture was heated for 3 hours under reflux and filtered hot from the triethylamine hydrochloride that had formed. The cooled filtrate was combined with petroleum ether and the crystals which formed after a short period of time were filtered off with suction. After two recrystallizations from methanoldimethylformamide, there was obtained pure N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - 3 - cyclohexyl - parabanic acid melting at 211—212°C.

b) 0.5 Grams of the substance obtained as described under paragraph (a) were heated for 45 minutes on a steam bath with 5 millilitres of dioxan and 10 millilitres of 1N-sodium hydroxide solution. The whole was then combined with water, acidified and the precipitate obtained was recrystallized from methanol. The N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea so obtained melted at 170—171°C.

EXAMPLE 8

N-[4-(β-<2-methoxy-5-bromo-benzamido>-ethyl)-benzenesulphonyl]-N'-(4-methyl-cyclohexyl)-urea (trans)

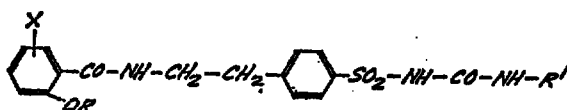
a) 17 Grams of N - [4 - (β - aminoethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea were stirred for 12 hours at 35—40°C with 8.6 grams of 2-methoxybenzoic acid chloride and 9 grams of pyridine in 100 millilitres of chloroform. The whole was concentrated under reduced pressure, the residue was dissolved in a 1% soda solution, the by-products that had formed were separated by etherification and the soda-alkaline layer was acidified with dilute hydrochloric acid. The resulting N - [4 - (β - <2 - methoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea was recrystallized from methanol and melted at 179—180°C.

b) 9.5 Grams of the urea obtained as described under paragraph (a) were suspended in 100 millilitres of glacial acetic acid; 1.3 millilitres of bromine were added dropwise to this suspension. The reaction mixture dissolved at first; later on, however, crystals separated out. The whole was heated for 1 hour at 40°C, then nitrogen was passed for 1 hour through the reaction mixture, and the reaction pro-

duct that had precipitated was separated by filtration with suction and recrystallized from methanol. The resulting N - [4 - (β - <2 - methoxy - 5 - bromo - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans) melted at 190—191°C.

WHAT WE CLAIM IS:—

1. A compound of the general formula



in which

R represents a lower alkyl or lower alkenyl group,

X represents a halogen atom or a lower alkyl or lower alkoxy group, and

R' represents a cyclohexyl, methylcyclohexyl or ethylcyclohexyl group or an endo-methylene-cyclohexenylmethyl or endomethylene-cyclohexylmethyl group.

2. A physiologically tolerable salt of a compound as claimed in claim 1.

3. A compound as claimed in claim 1, wherein R represents a methyl group.

4. A compound as claimed in claim 1 or 3, wherein X represents a chlorine atom or a methyl or methoxy group.

5. A compound as claimed in any one of claims 1, 3 and 4, wherein R represents a methylcyclohexyl or ethylcyclohexyl group in which the methyl or ethyl group is in the 4-position of the cyclohexyl group.

6. A physiologically tolerable salt of a compound as claimed in any one of claims 3 to 5.

7. N - [4 - (β - <2,5 - dimethoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea.

8. N - [4 - (β - <2,5 - dimethoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea.

9. N - [4 - (β - <2 - methoxy - 5 - fluoro - benzamido> - benzenesulphonyl] - N' - cyclohexyl - urea.

10. N - [4 - (β - <2 - methoxy - 5 - fluoro - benzamido> - ethyl) - benzene-sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea.

11. N - [4 - (β - <2 - methoxy - 5 - bromo - benzamido> - ethyl) - benzene-sulphonyl] - N' - cyclohexyl urea.

12. N - [4 - (β - <2 - methoxy - 5 - bromo - benzamido> - ethyl) - benzene-sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans).

13. N - [4 - (β - <2 - ethoxy - 5 - chloro - benzamido> - ethyl) - benzene-sulphonyl] - N' - cyclohexyl - urea.

14. N - [4 - (β - <2 - ethoxy - 5 - chloro - benzamido> - ethyl) - benzene-sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea.

15. N - [4 - (β - <2 - allyloxy - 5 - chloro - benzamido> - ethyl) - benzene-sulphonyl] - N' - cyclohexyl - urea.

16. N - [4 - (β - <2 - allyloxy - 5 - chloro - benzamido> - ethyl) - benzene-sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea.

17. N - [4 - (β - <2 - methoxy - 4 - chloro - benzamido> - ethyl - benzene-sulphonyl] - N' - cyclohexyl - urea.

18. N - [4 - (β - <2 - methoxy - 4 - chloro - benzamido> - ethyl) benzene-sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans).

19. N - [4 - (β - <2 - methoxy - 5 - methyl - benzamido> - ethyl) - benzene-sulphonyl] - N' - cyclohexyl - urea.

20. N - [4 - (β - <2 - methoxy - 5 - methyl - benzamido> - ethyl) - benzene-sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans).

21. N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzene-sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans).

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

23. Any one of the compounds as claimed in claim 1 and described in the Examples herein.

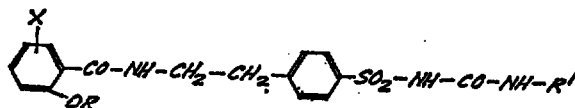
24. A physiologically tolerable salt of the compound claimed in any one of claims 7 to 22.



duct that had precipitated was separated by filtration with suction and recrystallized from methanol. The resulting N - [4 - (β - <2 - methoxy - 5 - bromo - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans) melted at 190—191°C.

WHAT WE CLAIM IS:—

1. A compound of the general formula



in which

R represents a lower alkyl or lower alkenyl group,

X represents a halogen atom or a lower alkoxy group, and

R¹ represents a cyclohexyl, methylcyclohexyl or ethylcyclohexyl group or an endo-methylene-cyclohexenylmethyl or endomethylene-cyclohexylmethyl group.

2. A physiologically tolerable salt of a compound as claimed in claim 1.

3. A compound as claimed in claim 1, wherein R represents a methyl group.

4. A compound as claimed in claim 1 or 3, wherein X represents a chlorine atom or a methyl or methoxy group.

5. A compound as claimed in any one of claims 1, 3 and 4, wherein R represents a methylcyclohexyl or ethylcyclohexyl group in which the methyl or ethyl group is in the 4-position of the cyclohexyl group.

6. A physiologically tolerable salt of a compound as claimed in any one of claims 3 to 5.

7. N - [4 - (β - <2,5 - dimethoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea.

8. N - [4 - (β - <2,5 - dimethoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea.

9. N - [4 - (β - <2 - methoxy - 5 - fluoro - benzamido> - benzenesulphonyl] - N' - cyclohexyl - urea.

10. N - [4 - (β - <2 - methoxy - 5 - fluoro - benzamido> - ethyl) - benzene-sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea.

11. N - [4 - (β - <2 - methoxy - 5 - bromo - benzamido> - ethyl) - benzene-sulphonyl] - N' - cyclohexyl urea.

12. N - [4 - (β - <2 - methoxy - 5 - bromo - benzamido> - ethyl) - benzene-sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans).

13. N - [4 - (β - <2 - ethoxy - 5 - chloro - benzamido> - ethyl) - benzene-sulphonyl] - N' - cyclohexyl - urea.

14. N - [4 - (β - <2 - ethoxy - 5 - chloro - benzamido> - ethyl) - benzene-sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea.

15. N - [4 - (β - <2 - allyloxy - 5 - chloro - benzamido> - ethyl) - benzene-sulphonyl] - N' - cyclohexyl - urea.

16. N - [4 - (β - <2 - allyloxy - 5 - chloro - benzamido> - ethyl) - benzene-sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea.

17. N - [4 - (β - <2 - methoxy - 4 - chloro - benzamido> - ethyl - benzene-sulphonyl] - N' - cyclohexyl - urea.

18. N - [4 - (β - <2 - methoxy - 4 - chloro - benzamido> - ethyl) benzene-sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans).

19. N - [4 - (β - <2 - methoxy - 5 - methyl - benzamido> - ethyl) - benzene-sulphonyl] - N' - cyclohexyl - urea.

20. N - [4 - (β - <2 - methoxy - 5 - methyl - benzamido> - ethyl) - benzene-sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans).

21. N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzene-sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans).

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

23. Any one of the compounds as claimed in claim 1 and described in the Examples herein.

24. A physiologically tolerable salt of the compound claimed in any one of claims 7 to 22.



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25. A physiologically tolerable salt of a compound as claimed in claim 23.
26. A pharmaceutical preparation suitable for the treatment of diabetes mellitus, which comprises a compound as claimed in any one of claims 1 and 3 to 5, in admixture or conjunction with a pharmaceutically suitable carrier.
27. A pharmaceutical preparation suitable for the treatment of diabetes mellitus, which comprises a physiologically tolerable salt as claimed in claim 2 or 6, in admixture or conjunction with a pharmaceutically suitable carrier.
28. A pharmaceutical preparation suitable for the treatment of diabetes mellitus, which comprises the compound claimed in any one of claims 7 to 22, in admixture or conjunction with a pharmaceutically suitable carrier.
29. A pharmaceutical preparation suitable for the treatment of diabetes mellitus, which comprises a physiologically tolerable salt as claimed in claim 24, in admixture or conjunction with a pharmaceutically suitable carrier.
30. A pharmaceutical preparation suitable for the treatment of diabetes mellitus, which comprises a compound as claimed in claim 23, in admixture or conjunction with a pharmaceutically suitable carrier.
31. A pharmaceutical preparation suitable for the treatment of diabetes mellitus, which comprises a physiologically tolerable salt as claimed in claim 25, in admixture or conjunction with a pharmaceutically suitable carrier.
32. A pharmaceutical preparation as claimed in any one of claims 26 to 31, which is in a form suitable for oral administration.
33. A pharmaceutical preparation as claimed in any one of claims 26 to 32, which is in unit dosage form.
34. A pharmaceutical preparation as claimed in claim 33, which is in the form of a tablet.
35. A pharmaceutical preparation as claimed in claim 33 or 34, which contains 0.5 to 100 milligrams of the active substance, per dosage unit.
36. A pharmaceutical preparation as claimed in claim 35, which contains 2 to 10 milligrams of the active substance, per dosage unit.
37. A process for the manufacture of a compound as claimed in claim 1 or 2, conducted substantially as described herein.
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Page 9, line 6, *after* hyphen (1st occurrence)
insert "N."

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30th June 1969

ERRATUM

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SLIP 2

Page 1, for Index at Acceptance C2C only read:-

(1J1A3, 1J1A6, 1J1A9, 1J1B, 1J1C2, 1J1D, 1J1E, 1J3C3, 1Q5, 1Q6B2, 1Q8A, 1Q9A, 1Q9F1, 1Q9H, 1Q11J, 2D43B, 2D43F, 2D43L, 2D43S3, 2D43Z1, 22Y, 220, 21, 225, 227, 31Y, 315, 34Y, 342, 36Y, 364, 385, 79Y, 790, JA)

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