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PATENT SPECIFICATION

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NO DRAWINGS

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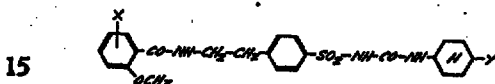
COMPLETE SPECIFICATION

Benzenesulphonyl-Ureas and process for their manufacture

We, FARBWERKE HOECHST AKTIENGESellschaft, 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 with bases, for example sodium salts. The new benzenesulphonyl-ureas in the free form or in the form of their physiologically tolerable salts with bases, possess blood sugar lowering properties and are distinguished by a strong and long-lasting hypoglycemic activity.

In the above general formula

25 X represents a chlorine or bromine atom or a methyl group linked to the 4- or 5-position with respect to the carboxylic amide group, preferably a chlorine atom, and

30 Y represents a hydrogen atom or a methyl group.

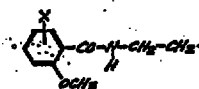
35 If the symbol represents a methyl group, this group may be in the cis- as well as in the trans-position to the urea group, the position not having an essential influence on the activity of the compounds. In most cases, the trans-configuration is prevalent in the end-product when a mixture of cis- and trans-methyl-cyclohexyl amine or of a derivative thereof is used as starting material.

40 The present invention also provides pro-

[Price 4s. 6d.]

cesses for the manufacture of the new benzenesulphonyl-ureas and their physiologically tolerable salts with bases. According to these processes, the compounds can be prepared by

(a) reacting benzenesulphonyl isocyanates, benzenesulphonyl carbamic acid esters, benzenesulphonyl thiolcarbamic acid esters, benzenesulphonyl ureas, or benzenesulphonyl-semicarbazides or -semicarbazones carrying the substituent

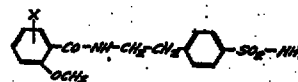


in the p-position with



substituted amines or their salts;

(b) reacting sulphonamides of the formula



or their salts with



substituted isocyanates, carbamic acid esters, thiolcarbamic acid esters, carbamic acid halides or ureas;

(c) hydrolysing correspondingly substituted benzenesulphonyl-isourea ethers, -isourea esters, -isothiourea ethers, -parabanic acids or -haloformic acid amidines,

(d) adding water on to correspondingly substituted carbodiimides;

(e) replacing the sulphur atom in correspondingly substituted benzenesulphonyl-thio-ureas by an oxygen atom;

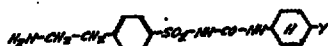
(f) hydrogenating correspondingly substituted benzenesulphonyl-ureas containing in the molecule an unsaturated linkage, or

(g) introducing by acylation the radical,

Price 5s. 0d.



if desired in one or several steps, into benzenesulphonyl-ureas of the formula



- 5 and, if desired, converting a resulting compound into a physiologically tolerable salt thereof by treatment with a base, for example an alkaline agent.

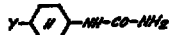
- 10 The benzenesulphonyl-carbamic acid esters or -thiocarbamic acid esters mentioned may contain, in the alcohol component, an alkyl or aryl group or also a heterocyclic group. Because this group is split off in the reaction, its chemical constitution does not influence the nature of the final product and it may therefore be varied within wide limits. The same applies to carbamic acid esters which carry the substituent



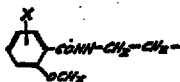
- 20 or the corresponding thiolcarbamic acid esters. As carbamic acid halides, the chlorides are advantageously used.

- 25 The benzenesulphonyl-ureas used as starting materials in the process of the present invention may be unsubstituted at the terminal amino group or they may be mono- or di-substituted. Because these substituents are split off in the reaction with amines, their nature may be varied within wide limits. In addition to benzenesulphonyl-ureas carrying alkyl, aryl, acyl or heterocyclic substituents, there may also be used bis - (benzenesulphonyl) - ureas which may carry, at one of the nitrogen atoms, an additional substituent, for example a methyl group. For example, bis - (benzenesulphonyl)-ureas or also N - benzenesulphonyl - N' - acyl - ureas may be treated with cyclohexyl amine or 4 - methyl - cyclohexyl amine and the salts obtained may be heated to elevated temperatures, in particular to temperatures above 100°C.

It is furthermore possible to start from ureas of the formula



- 45 or from ureas which may carry, at the free nitrogen atom, one or preferably two substituents, and to react these with benzenesulphonyl-amides carrying the substituent



- 50 As such starting materials, there may be mentioned, for example, N-cyclohexyl- or N-(4-methyl-cyclohexyl)-urea, corresponding N'-

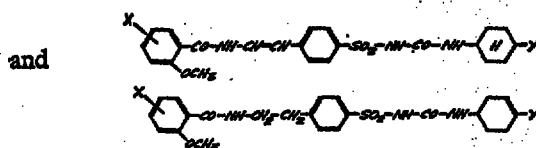
acetyl-ureas, N'-nitro-ureas, N'-cyclohexyl-ureas, N' - (4 - methyl - cyclohexyl) - ureas, N',N' - diphenyl - ureas (in which the two phenyl groups may also carry substituents or may be linked to each other directly or via a bridge member such as $-\text{CH}_2-$, $-\text{NH}-$, $-\text{O}-$, or $-\text{S}-$), N' - methyl - N' - phenyl - ureas, N',N' - dicyclohexyl - ureas as well as Y-substituted cyclohexyl - carbamoyl - imidazoles or -triazoles.

It is advantageous to hydrolyse the benzenesulphonylparabanic acids, -isourea ethers, -isothiurea ethers, -isourea esters or -haloformic acid amidines mentioned as starting materials, in an alkaline medium. Isourea ethers and isourea esters can also be hydrolysed successfully in an acidic medium.

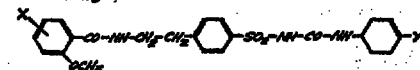
In correspondingly substituted benzenesulphonylthioureas, the sulphur atom may be replaced by the oxygen atom in a known manner, for example, with the aid of oxides or salts of heavy metals or by using oxidizing agents such as hydrogen peroxide, sodium peroxide or nitrous acid.

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.

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



and



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

Amino-ethyl-benzenesulphonyl-ureas may be acylated either in one step, for example by reaction of correspondingly substituted benzoic acid halides, or in several steps. As one example among many others of a multi-step acylation, there may be mentioned the reaction of aminoethyl-benzenesulphonyl-ureas with 2-methoxy-benzoyl chloride and the subsequent introduction of a halogen atom into the benzene nucleus of the benzamido group.

With regard to the reaction conditions, the manner of carry 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.

Depending on the nature of the starting

materials, one or another of the processes hereinbefore described may, in some cases, produce a desired individual benzenesulphonyl-urea only in small yields or it may be inappropriate for its synthesis. In such comparatively rare cases, the expert has no difficulties in synthesizing the desired product according to another of the processes described.

Our Specification No. 1,080,705 describes and claims benzene-sulphonyl-ureas of the general formula



in which

- 15 R represents a hydrogen atom or a lower alkyl or phenyl-lower alkyl group, R' represents
- (a) an alkyl, an alkenyl or a mercaptoalkyl group, each containing 2 to 8 carbon atoms,
- 20 (b) an alkoxyalkyl, alkylmercaptoalkyl or alkylsulphinylalkyl group, each containing 4 to 8 carbon atoms and at least two of which carbon atoms form the alkylene portion of the alkoxyalkyl, alkylmercaptoalkyl or alkylsulphinyl-alkyl group,
- 25 (c) a phenyl-lower alkyl or phenyl-cyclopropyl group,
- (d) a cyclohexyl-lower alkyl, cycloheptylmethyl, cycloheptylethyl or cyclooctylmethyl group,
- (e) an endoalkylene cyclohexyl, endoalkylene cyclohexenyl, endoalkylene cyclohexenylmethyl or endoalkylene cyclohexenylmethyl group, each containing 1 or 2 endoalkylene carbon atoms,
- 35 (f) a lower cyclohexyl or lower alkoxy cyclohexyl group,
- (g) a cycloalkyl group containing 5 to 8 carbon atoms,
- 40 (h) a cyclohexenyl or cyclohexenylmethyl group,
- (i) a heterocyclic ring containing 4 or 5 carbon atoms, 1 oxygen or sulphur atom and which may contain up to 2 ethylenic double bonds, or
- 45 (j) a heterocyclic ring as defined under (i) which is attached to the adjacent nitrogen atom via a methylene group,
- 50 X represents a single chemical bond or an aliphatic or a cycloaliphatic hydrocarbon bridge containing 1 to 6 carbon atoms and which may contain one —O— or —S— atom or one —SO— or —SO₂— group,
- 55 Y represents a hydrocarbon group containing 1 to 4 carbon atoms,
- Z represents a hydrogen or halogen atom or a lower alkyl or lower alkoxy group,

a cycloalkoxy group containing 5 or 6 carbon atoms, a cyclohexyl, lower alkyl mercapto lower alkyl sulphinyl, lower alkyl sulphonyl, phenylsulphonyl, phenyl, phenyl-lower alkyl, lower acyl, benzoyl, trifluoromethyl, hydroxyl, lower acyloxy, benzyloxy, carboxyl, lower carbalkoxy, nitrile, carbamyl, lower alkyl carbamyl, lower dialkyl carbamyl or nitro group,

Z' and Z'' each represents a hydrogen atom or — if Z represents a hydrogen or halogen atom or a hydroxyl, carboxyl, alkyl or alkoxy group — each may also represent a lower alkyl or lower alkoxy group or a halogen atom or — if Z represents a hydrogen atom — Z' and Z'' may also together represent a methylenedioxy group of the formula —O—CH₂—O—, and the phenylene group is unsubstituted or substituted by one or more substituents selected from halogen atoms, lower alkyl groups and alkoxy groups, and their physiologically tolerable salts with bases, a process for their manufacture and pharmaceutical preparations containing these compounds.

The combination of properties possessed by the benzenesulphonyl-ureas of the present invention, some details of which are given below, make them superior to the benzenesulphonyl-ureas described and claimed in Specification No. 1,080,705.

The hypoglycemic action of several of the compounds of the present invention can be seen from the following Tables in which

- I represents N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea, 100
- II represents N - [4 - (β - <2 - methoxy - 4 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methylcyclohexyl) - urea, 105
- III represents N - [4 - (β - <2 - methoxy - 5 - methyl - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methylcyclohexyl) - urea, 110
- IV represents N - [4 - (β - <2 - methoxy - 5 - bromo - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methylcyclohexyl) - urea, and 115
- V represents N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methylcyclohexyl) - urea. 120



TABLE 1

Limit dose — see footnote below — (in mg/kg of body weight)
in several test animals

Compound	Rabbit	Dog	Rat
I	0.025	0.02	0.1
II	0.08	0.04	0.6
III	0.02	0.01	0.05
IV	0.08	0.01	0.03
V	0.02	0.01	0.06

TABLE 2

Period of action in rabbits (dose: 10 mg/kg of body weight)

Compound

Lowering of the blood sugar level (in %), compared to the original value, after the number of hours indicated in the heading

	3	24	48	72	96	106
I	19	23	28	13		0
II	26	24	0			
III	37	21	28	19		
IV	24	30	35	21	0	
V	15	27	19		0	

The period of action in dogs (dose administered: 10 mg/kg of body weight) is about 24 hours for compounds I to V.

The low acute toxicity results of some compounds, given as examples, are shown in the following Table 3:

TABLE 3
LD₅₀ in mice (in g/kg of body weight) *per os*

Compound	LD ₅₀
I	3.25
III	3.0
IV	9.0
V	4.5

Limit dose: the dose which is capable of lowering the blood sugar level by about 10%, after having been administered once in the form of the sodium salt.

- 5 In humans who are not suffering from metabolic diseases, a limit dose of 15 g/kg has been ascertained for compound I. For comparison's sake, the hitherto known N - (4 - methylbenzenesulphonyl) - N' - butyl - urea has a limit dose of 7,000 g/kg in humans who are not suffering from metabolic diseases.

- 10 Analogous to the known N - (4 - methyl - benzenesulphonyl) - N' - butyl - urea, the compounds of the present invention have no effect on animals without a pancreas.

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

- 20 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 with bases 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 hydroxides or alkaline earth metal hydroxides, or alkali metal or alkaline earth metal carbonates or bicarbonates.

- 35 The pharmaceutical preparations are advantageously in the form of tablets which contain in addition to the compounds of the present invention, the pharmaceutically suitable adjuvants and carriers, for example talc, starch, lactose, tragacanth or magnesium stearate.

- 40 A pharmaceutical preparation containing one of the new benzenesulphonyl-ureas or physiologically tolerable salts with bases as active substance, for example a tablet or a powder, with or without the aforesaid additives, 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.

- 55 The following Examples illustrate some of the numerous processes that may be used for the synthesis of the benzenesulphonyl-ureas of the present invention.

- 60 In most cases, the methods of synthesis are described for N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea. The rest

invention falling within the general formula given above, are prepared in an analogous manner with the use of correspondingly substituted starting materials.

EXAMPLE 1

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

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 mixture 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 was obtained: N - [4 - (β - <2 - methoxy - 5 - methyl - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 157—159°C (from methanol).

EXAMPLE 2

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

2.45 Grams of N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - phenyl - urethane (obtained from 4 - [β - (2 - methoxy - 5 - chloro - benzamido) - ethyl] - benzenesulphonamide and chloroformic acid phenyl ester) were refluxed for 2 hours with 0.5 gram of cyclohexylamine in 30 ml of dioxan. After dilution with water and acidification with dilute hydrochloric acid, there was obtained a precipitate which was treated with ammonia of 0.5% strength. The aqueous alkaline solution was acidified and the precipitate obtained was recrystallized from methanol. N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea was obtained melting at 171—172°C.

EXAMPLE 3

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

4.26 Grams of N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - methyl - urethane were heated on a descending condenser for 1½ hours with 1.6 grams of cyclohexylamine acetate in 100 ml of dioxan.

After the addition of water and recrystallization



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ation of the product which had precipitated, from methanol, there was obtained a very good yield of N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea melting at 172—173°C.

EXAMPLE 4

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

A mixture of 10.3 grams of N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - urea (melting point 171—173°C), 300 millilitres of toluene, 30 millilitres of glycolmonomethyl 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 - <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 was obtained: N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 189—190°C (from methanol).

EXAMPLE 5

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

1.06 Grams of N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - methyl - urea (melting point 197—198°C), which had been obtained from N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - methyl - urethane and methyl amine, and 0.5 gram of cyclohexyl amine were refluxed for 1½ hours in 30 ml of dioxan. After the addition of water and acidification with dilute hydrochloric acid and recrystallization of the product from methanol, there was obtained a good yield of N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl-urea melting at 171—172°C.

EXAMPLE 6

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

4.9 Grams of N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - phenyl - urea (melting point 193—195°C), 100 ml of dioxan and 1 gram of cyclohexyl amine were refluxed at the boil for 1 hour.

The clear solution was then concentrated under reduced pressure and the residue obtained was treated with ammonia of about 0.5% strength. After having been clarified by

filtration the solution was acidified. The precipitate of N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea obtained was filtered off with suction and dried on clay. After recrystallization from methanol, a pure product melting at 170—172°C was obtained.

EXAMPLE 7

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

a) 5 Grams of N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - urea were suspended in 30 ml of acetic acid anhydride. 5 Drops of concentrated sulphuric acid were added and the whole was heated for 5 minutes on a steam bath. The substance passed into solution and then it precipitated in crystals. When the mixture was cool, the crystals obtained were filtered off with suction, washed with ethyl acetate and dried. After a short boil with methanol, the N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - acetyl - urea so obtained melted at 208°C with decomposition.

b) 2.3 Grams of the product obtained as described under paragraph (a) and 0.5 gram of cyclohexyl amine were carefully mixed. Under the evolution of heat, the cyclohexylamine salt of N - [4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonyl] - N' - acetyl - urea formed. The salt was filled into an Erlenmeyer flask and heated at 150°C in an oil bath for 45 minutes. After some minutes, the salt melted while forming a clear melt.

The whole was allowed to cool, the reaction product was treated with aqueous ammonia of 0.5% strength while being heated on a steam bath, it was then filtered and the filtrate was acidified. The crystalline precipitate was filtered off with suction and once more taken up in ammonia of 0.5% strength.

By the acidification of the filtrate there was obtained a crystalline precipitate of N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl-urea which was filtered off with suction and dried. After recrystallization from methanol, the substance melted at 169—170°C.

EXAMPLE 8

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

2.4 Grams of N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N',N' - pentamethylene - urea (melting point 181—183°C) from 1 gram of cyclohexyl amine were refluxed for 2 hours in 35 ml of dioxan. After the whole had been acidified with dilute hydrochloric acid and the precipitate obtained had been recrystallized



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from methanol, there was obtained a good yield of N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl-urea melting at 172—173°C.

EXAMPLE 9

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

- 10 6.5 Grams of the sodium salt of 4 - [β - (2 - methoxy - 5 - chloro - benzamido) - ethyl] - benzenesulphonamide were refluxed for 3 hours with 3.9 grams of diphenyl carbamic acid chloride in 60 ml of toluene. The crude N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N',N'-diphenyl - urea so formed was filtered off with suction and suspended in dioxan. After the addition of 1 gram of acetic acid and 1.8 grams of cyclohexylamine the whole was refluxed for 1½ hours. After acidification with dilute hydrochloric acid, the precipitate was filtered off with suction and treated with ammonia of 0.5% strength. The aqueous alkaline solution was acidified and the crystals were recrystallized from methanol.

- 25 N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea was obtained melting at 170—171°C.

EXAMPLE 10

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

- 35 a) 10 Grams of the sodium salt of 4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonamide and 10.8 grams of N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - carbamic acid methyl ester were mixed and the mixture was heated for 30 minutes in an oil bath which had been heated to 175°C. The sintered substance was cooled and treated with aqueous ammonia of about 0.5% strength. The substance was then filtered and acidified. The precipitate was filtered off with suction and then once more taken up in ammonia of 0.5% strength. After another acidification with hydrochloric acid, the precipitate was filtered off with suction and dried on clay. After a treatment with ethyl acetate and a boil with ethanol, there was obtained N,N' - bis - 4 - [β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - urea melting at 183—185°C.

- 55 b) 0.95 Gram of the compound obtained as described under paragraph (a) was suspended in 30 ml of dioxan. 0.125 gram of cyclohexylamine was added and the whole was refluxed at the boil for 1 hour. After the clear solution obtained had been concentrated it was treated with aqueous ammonia of 0.5% strength. Some 4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesul-

phonamide which precipitated was filtered off and the resulting clear filtrate was acidified. There was obtained a crystalline precipitate of N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea, which was filtered off with suction, dried and recrystallized from methanol. Melting point 168—170°C.

EXAMPLE 11

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

4.95 Grams of 4 - [β - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - 1,1 - pentamethylene - semicarbazide (melting point 165—167°C), 50 ml of dioxan and 1 gram of cyclohexyl amine were refluxed at the boil for 45 minutes. The solution obtained was concentrated under reduced pressure and the residue was taken up in aqueous ammonia of about 0.5% strength. The whole was filtered and the filtrate was acidified. There was obtained a crystalline precipitate of N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea which was filtered off with suction and dried, first in air and then on a steam bath. After recrystallization from methanol, the substance melted at 168—170°C.

The same substance was obtained by heating at 120°C, for 1 hour, 3.3 grams of 4 - [β - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - 1 - acetyl - semicarbazide (melting point 181—183°C) in 50 ml of dimethyl formamide and 0.73 gram of cyclohexyl amine, and by treating the whole in the same manner as described above.

EXAMPLE 12

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

A reaction mixture of 1.8 grams of 4 - [β - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - cyclooctanone - semicarbazone of melting point 180—182°C (prepared by heating the sodium salt of 4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonamide with cyclooctanone-semicarbazone in dimethyl formamide at 100°C for 4 hours), 50 ml of dioxan and 0.33 gram of cyclohexyl amine was refluxed at the boil for 1 hour. The clear solution was concentrated under reduced pressure and the residue obtained was treated with aqueous ammonia of about 0.5% strength. After filtration, the filtrate was acidified. There was obtained a crystalline precipitate of N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea, which was filtered off with suction, dried and recrystallized from methanol. The substance melted at 168—170°C.

EXAMPLE 13

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

- 5 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 cyclohexylisocyanate 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.
- 10 In analogous manner there were obtained: from 4 - (β - <2 - methoxy - 5 - bromo - benzamido> - ethyl) - benzenesulphonamide (melting point 223—224°C):
- 15 N - [4 - (β - <2 - methoxy - 5 - bromo - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea, melting at 161—163°C (from methanol), and
- 20 N - [4 - (β - <2 - methoxy - 5 - bromo - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting at 187—189°C (from methanol); from 4 - (β - <2 - methoxy - 4 - chloro - benzamido> - ethyl) - benzenesulphonamide (melting point 187—188°C):
- 25 N - [4 - (β - <2 - methoxy - 4 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea, melting at 200—201°C (from methanol/dimethyl formamide) and
- 30 N - [4 - (β - <2 - methoxy - 4 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting at 204—205°C (from methanol/dimethyl formamide);
- 35 from 4 - (β - <2 - methoxy - 4 - bromo - benzamido> - ethyl) - benzenesulphonamide (melting point 202—203°C):
- 40 N - [4 - (β - <2 - methoxy - 4 - bromo - benzamido> - ethyl) benzenesulphonyl] - N' - cyclohexyl - urea, melting at 201—203°C (from methanol/dimethyl formamide) and
- 45 N - [4 - (β - <2 - methoxy - 4 - bromo - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans) melting at 205—206°C (from methanol/dimethyl formamide);
- 50 from 4 - (β - <2 - methoxy - 4 - methyl - benzamido> - ethyl) - benzenesulphonamide (melting point 188—189°C):
- 55 N - [4 - (β - <2 - methoxy - 4 - methyl - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea, melting at 209—211°C (from methanol/dimethyl formamide), and
- 60 N - [4 - (β - <2 - methoxy - 4 - methyl - benzamido> - ethyl) - benzenesulphonyl] -

N' - (4 - methylcyclohexyl) - urea (trans), melting at 208—209°C (from methanol/dimethyl formamide).

EXAMPLE 14

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

3.9 Grams of the sodium salt of 4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonamide and 4.4 grams of N - cyclohexyl - carbamic acid phenyl ester were dissolved in 100 ml of dimethyl formamide. The solution was heated at 110°C for 45 minutes, it was allowed to cool and then poured into aqueous ammonia of about 0.5% strength. The insoluble portion is filtered off and the filtrate was acidified. The crystalline precipitate of N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea was filtered off with suction, washed and dried. After recrystallization from methanol, the substance melted at 168—170°C.

EXAMPLE 15

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

1.95 Grams of the sodium salt of 4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonamide and 1.6 grams of N - cyclohexyl - monothiocarbamic acid S-methyl ester (prepared by the methylation of the potassium salt of N - cyclohexyl - monothiocarbamic acid with dimethyl sulphate, melting point: 110—112°C) were triturated together in a mortar and the whole was heated at 180°C for 13 minutes in an Erlenmeyer flask. The reaction mixture first became oily and then solidified again. The mixture was treated with aqueous ammonia of 0.5% strength, the insoluble portion was filtered and the filtrate was acidified. The precipitate obtained was filtered off with suction and was once more purified by dissolving it in dilute ammonia and precipitating it with acid. The substance was filtered off with suction and dried. After recrystallization from methanol, there was obtained N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea melting at 168—170°C.

EXAMPLE 16

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

3.9 Grams of the sodium salt of 4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonamide and 4.26 grams of cyclohexylurea were carefully mixed in a mortar and the mixture was heated in an Erlenmeyer flask for 10 minutes in an oil bath which had been preliminarily heated to 200°C.

(trans),
nol/di-

ido>- 70
xyl-

- (β -
ido> -
grams 75
yl ester
l form-
0°C for
nd then
at 0.5% 80
red off
stalline
thoxy -
enzene-
was fil- 85
d. After
stance

ido>- 90
xyl-

4 - (β -
ido> -
grams of 95
acid. Sa-
tion of
mono-
ulphate,
ituated 100
s heated
enmeyer
me oily
are was
0.5% 105
red and
bate ob-
nd was
n dilute
id. The 110
ion and
ethanol,
- meth-
l) - ben-
ea melt- 115

ido>-
xyl- 120

4 - (β -
ido> -
6 grams
ed in a
n Erlen- 125
oil bath
, 200°C.

After cooling, the melt was warmed on a steam bath with ammonia of about 0.5% strength. The substance was filtered and the filtrate was slightly acidified. The precipitate obtained was filtered off with suction and once more taken up in ammonia of 0.5% strength. After the filtrate had been once more acidified, the precipitate of N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea so obtained was filtered off with suction, dried and recrystallized from methanol.

The substance melted at 167—169°C and it showed no depression of the melting point when mixed with the same substance obtained according to a different method.

EXAMPLE 17

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

3.9 Grams of the sodium salt of 4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonamide and 3.7 grams of N - acyl - N' - cyclohexyl - urea were heated at 110°C for 2 hours in 100 ml of dimethyl formamide. The solution obtained was concentrated under reduced pressure to 2/3 of its volume and then water and hydrochloric acid were added thereto. The solid material was filtered off with suction and treated with aqueous ammonia of 0.5% strength. After filtration, the filtrate was acidified and the precipitate of N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea so obtained was filtered off with suction, washed and dried. After recrystallization from methanol, there was obtained N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea melting at 168—170°C.

EXAMPLE 18

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

3.8 Grams of the sodium salt of 4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonamide and 0.5 gram of anhydrous sodium carbonate were heated while stirring in a mixture of 25 ml of xylene and 8 ml of dioxan, until the solvent started to boil. A solution of 1.7 grams of N - nitro - N' - cyclohexyl - urea (melting point 132°C) in 5 ml of xylene and 1 ml of dioxan was then slowly added dropwise thereto. After stirring has been continued for 3 hours, the substance was cooled, filtered off with suction and the precipitate was treated with 2N hydrochloric acid in a mortar. The substance was then extracted with ammonia of 1% strength, and was then acidified and recrystallized from methanol. The sulphonyl-urea melted at 170—172°C.

EXAMPLE 19

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

3.9 Grams of the sodium salt of 4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonamide, 5.9 grams of N,N - diphenyl - N' - cyclohexyl - urea and 100 ml of dimethyl formamide were heated at 110°C for 45 minutes. (After some minutes, the whole formed a clear solution). The solution was allowed to cool, was poured into water and ammonia of 0.5% strength was added thereto. After filtration, the filtrate was acidified. The precipitate obtained was filtered off with suction and, once more, ammonia of 0.5% strength was added thereto. After filtration and acidification of the filtrate, there was obtained a crystalline precipitate of N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea, which was filtered off with suction, washed and dried, first in air and then in a drying chamber at 60°C.

After recrystallization from methanol, the substance melted at 170—172°C.

EXAMPLE 20

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

3.9 Grams of the sodium salt of 4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonamide and 4.7 grams of N - phenyl - N - methyl - N' - cyclohexyl - urea were carefully mixed in a mortar, then the mixture was filled into an Erlenmeyer flask and introduced for 10 minutes into an oil bath which had been preliminarily heated to 200°C. After cooling, the clear melt was treated with ammonia of 0.5% strength on a steam bath. The insoluble portion was filtered off, the filtrate was acidified and the precipitate obtained was filtered off with suction. When the precipitate had once more been treated with ammonia of 0.5% strength and then filtered, there was obtained from the filtrate, after acidification, N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea which was filtered off with suction and dried. After recrystallization from methanol, the substance melted at 168—170°C.

EXAMPLE 21

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

2 Grams of the sodium salt of 4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonamide and 2.5 grams of N,N' - dicyclohexyl - urea were carefully mixed in a mortar. The mixture was filled into an Erlenmeyer flask and then heated at 220°C for 10 minutes in a pre-heated oil bath. After

cooling, the sintered reaction cake was treated with ammonia of 0.5% strength. After filtration, the filtrate was acidified. There was obtained a precipitate which was filtered off with suction and once more taken up in ammonia of 0.5% strength. After filtration, the filtrate was acidified. The precipitate of crude N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea obtained was filtered off with suction and dried in air. By treatment with methanol there was obtained a substance which was first oily and then crystalline and which was once more recrystallized from methanol after filtration with suction. The N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea so obtained melted at 169—171°C.

20 **EXAMPLE 22**
N-[4-(β -<2-methoxy-5-chloro-benzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea

25 3.9 Grams of the sodium salt of 4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonamide and 3.9 grams of N - imidazolyl - N' - cyclohexyl - urea (melting point 96—98°C) were added to 100 ml of dry tetrahydrofuran. The mixture was stirred and heated to about 85°C and then 30 70 ml of diethylformamide were added thereto, whereupon a solution formed.

When the reaction had been completed, the solution was poured into aqueous ammonia of 0.5% strength. The insoluble portion was filtered off and the filtrate was acidified. The precipitate obtained was filtered off with suction and dissolved in ammonia of 0.5% strength. By filtration and acidification of the filtrate, there was obtained a crystalline precipitate of N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea which was filtered off with suction, washed with water and dried. After recrystallization from methanol, the substance obtained melted at 170—172°C.

35 **EXAMPLE 23**
N-[4-(β -<2-methoxy-5-chloro-benzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea

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

45 74 Grams of 4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonamide were dissolved in 350 millilitres of dimethyl formamide. 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 to 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 isothiurea methyl ether 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.

50 **EXAMPLE 24**
N-[4-(β -<2-methoxy-5-chloro-benzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea

a) 4.9 Grams of N - 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 triethyl-

litres of 65
4 - (β -
ido> -
dithio-
was fil-
alcohol 70
y - 5 -
zenesul-
dimethyl 75
ained as
lissolved
de solu-
ate were
ion. The
30 min-
decant-
crystal-
ed from
grams of 85
chloro -
ionyl] -
yl ester
y - 5 - 90
zenesul-
methyle
as des-
olved in 95
f cyclo-
ole was
1. Upon
acidifi-
ve-indi- 100
obtained
y - 5 -
zenesul- 105
er para-
sodium
solution
h. After
id acidi- 110
- <2 -
ethyl) -
urea was
precipi-
inol, the 115
nido> -
exyl- 120
arabanic
re dis-
id com-
- meth- 125
l) - ben-
102 -
3 hours
triethyl-

amine 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 methanol/dimethylformamide, 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 Gram 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 25

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

a) 3 Grams of N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - thiourea, prepared by reacting 4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonamide with cyclohexyl-isothiocyanate in boiling acetone in the presence of potassium carbonate (melting point 168—170°C (from ethyl acetate) with decomposition), were suspended in 50 ml of a 2N-sodium hydroxide solution. 10 ml of hydrogen peroxide of 35% strength were then added. The whole was heated for 30 minutes on a steam bath, acidified with dilute hydrochloric acid, the crystalline precipitate obtained was filtered off with suction and was recrystallized from methanol. The isolated N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea melted at 170—172°C, after recrystallization from methanol.

The same compound was obtained by desulphurizing the thiourea mentioned above by a treatment with mercury oxide in the presence of a sodium hydroxide solution. For this purpose, 0.5 grams of the thiourea was dissolved in 10 ml of dioxan and 10 ml of a 2N sodium hydroxide solution. 0.22 Gram of mercury oxide was added and the whole was stirred for 4 hours at 40°C. The mercury sulphide which had formed, was filtered off with suction, the filtrate was acidified and the precipitate of N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea so obtained was filtered off with suction and recrystallized from methanol. Melting point 170—172°C.

b) 0.52 Gram of N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) -

benzenesulphonyl] - N' - cyclohexyl - thiourea were dissolved in 50 ml of methanol. 0.22 Gram of mercury oxide and a small amount of potassium carbonate were added while stirring and the whole was heated while stirring at 50—55°C for 3 hours. After the mercury oxide which had formed, had been filtered off, the solution was concentrated and N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl-isourea - methyl ether was obtained as a viscous resin. A sample of this isourea was covered with concentrated hydrochloric acid in a test tube and the whole was heated while stirring for some minutes on a steam bath. The crystalline substance of N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea obtained was recrystallized from methanol and had a melting point of 168—170°C.

EXAMPLE 26

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

5 Grams of N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - thiourea (melting point 168—170°C) were dissolved in 400 ml of absolute tetrahydrofuran. Dry phosgene was then introduced into the solution while stirring, and the temperature simultaneously rose from 25° to 33°C. After nitrogen had been passed through in order to remove the excess phosgene from the solution, the solution was concentrated under reduced pressure and at room temperature. A viscous resin was obtained as a residue. 2 Grams of this resin were covered with an excess of a 2N-sodium hydroxide solution and the whole was heated while stirring on a steam bath with a simultaneous addition of dioxan as a solution-promoter. After the insoluble portion had been filtered off, the filtrate was acidified and the precipitated N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea was filtered off with suction. It was dissolved in ammonia of 0.5% strength and then precipitated again. The product was filtered off, dried and then recrystallized from methanol. Melting point: 168—170°C.

EXAMPLE 27

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

2.5 Grams of N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - (A³ - cyclohexenyl) - urea (melting point 154—155°C), prepared from 4 - (β - <2 - methoxy - 5 - chlorobenzamido> - ethyl) - benzenesulphonamide and 3 - cyclohexenyl - isocyanate, were dissolved in 150 ml of methanol and in about 5 ml of dimethyl formamide and the solution was

hydrogenated in the presence of a palladium catalyst in a shaking device at room temperature and under normal pressure. When the absorption of hydrogen had ceased, the catalyst was filtered off with suction, the majority of the solvent was evaporated under reduced pressure, the residue was combined with water and the precipitated product was isolated by filtration with suction. The resulting N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea was dissolved and reprecipitated from a large amount of ammonia of 1% strength and it was recrystallized from methanol. Melting point: 167—168°C.

EXAMPLE 28

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

16.3 Grams of N - [4 - (β - amino - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea were suspended in 130 ml of chloroform. After the addition of 9 grams of pyridine, 10.3 grams of 2 - methoxy - 5 - chloro - benzoic acid chloride was introduced and the whole was heated while stirring at 40°C for 6 hours. The solution obtained was concentrated under reduced pressure and the oily residue was extracted with ammonia of 1% strength. After the alkaline solution had been acidified and the precipitate had been recrystallized, there was obtained N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea melting at 171—172°C.

EXAMPLE 29

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

a) 17 Grams of N - [4 - (β - amino - ethyl) - 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% sodium carbonate 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 - 5 - bromo - 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. The whole was heated for 1 hour at 40°C, then nitrogen was passed for

1 hour through the reaction mixture, and the reaction product 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.

EXAMPLE 30

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

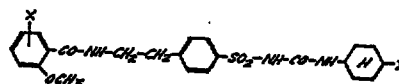
3.9 Grams of the sodium salt of 4 - (β - 2 - methoxy - 5 - chloro - benzamido - ethyl) - benzenesulphonamide, 6.12 grams of N,N - di-cyclohexyl - N' - cyclohexyl - urea (melting point 182—183°C) and 100 ml of dimethyl formamide were heated under reflux at 110°C in an oil bath. Water was added to the solution which was then filtered. The filtrate was acidified with dilute hydrochloric acid and the precipitate was filtered off with suction.

The product so obtained was dissolved and reprecipitated from aqueous ammonia of 0.5% strength and dilute hydrochloric acid and then dried.

After recrystallization from methanol, the substance melted at 168—170°C.

WHAT WE CLAIM IS:—

1. A benzenesulphonyl-urea of the general formula



in which X represents a chlorine or bromine atom or a methyl group linked to the 4- or 5-position to the carboxylic amide group, and Y represents a hydrogen atom or a methyl group.

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

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

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

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

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

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

8. A physiologically tolerable salt with a base of the compound claimed in claim 3.



hydrogenated in the presence of a palladium catalyst in a shaking device at room temperature and under normal pressure. When the absorption of hydrogen had ceased, the catalyst was filtered off with suction, the majority of the solvent was evaporated under reduced pressure, the residue was combined with water and the precipitated product was isolated by filtration with suction. The resulting N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea was dissolved and reprecipitated from a large amount of ammonia of 1% strength and it was recrystallized from methanol. Melting point: 167—168°C.

EXAMPLE 28

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

16.3 Grams of N - [4 - (β - amino - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea were suspended in 130 ml of chloroform. After the addition of 9 grams of pyridine, 10.3 grams of 2 - methoxy - 5 - chloro - benzoic acid chloride was introduced and the whole was heated while stirring at 40°C for 6 hours. The solution obtained was concentrated under reduced pressure and the oily residue was extracted with ammonia of 1% strength. After the alkaline solution had been acidified and the precipitate had been recrystallized, there was obtained N - [4 - (β - <2 - methoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea melting at 171—172°C.

EXAMPLE 29

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

a) 17 Grams of N - [4 - (β - amino - ethyl) - 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% sodium carbonate 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. The whole was heated for 1 hour at 40°C, then nitrogen was passed for

1 hour through the reaction mixture, and the reaction product 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.

EXAMPLE 30

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

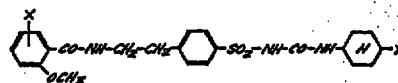
3.9 Grams of the sodium salt of 4 - (β - 2 - methoxy - 5 - chloro - benzamido - ethyl) - benzenesulphonamide, 6.12 grams of N,N - di-cyclohexyl - N' - cyclohexyl - urea (melting point 182—183°C) and 100 ml of dimethyl formamide were heated under reflux at 110°C in an oil bath. Water was added to the solution which was then filtered. The filtrate was acidified with dilute hydrochloric acid and the precipitate was filtered off with suction.

The product so obtained was dissolved and reprecipitated from aqueous ammonia of 0.5% strength and dilute hydrochloric acid and then dried.

After recrystallization from methanol, the substance melted at 168—170°C.

WHAT WE CLAIM IS:—

1. A benzenesulphonyl-urea of the general formula



in which X represents a chlorine or bromine atom or a methyl group linked to the 4- or 5-position to the carboxylic amide group, and Y represents a hydrogen atom or a methyl group.

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

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

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

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

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

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

8. A physiologically tolerable salt with a base of the compound claimed in claim 3.





9. The sodium salt of the compound claimed in claim 3.

10. A physiologically tolerable salt with a base of the compound claimed in any one of claims 4 to 7.

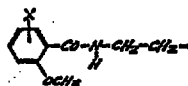
11. The sodium salt of the compound claimed in any one of claims 4 to 7.

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

13. A physiologically tolerable with a base salt of a compound as claimed in claim 12.

14. A process for the manufacture of a benzenesulphonyl-urea as claimed in claim 1 or a physiologically tolerable salt thereof with a base, which comprises

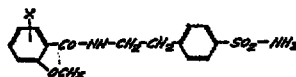
a) reacting a benzenesulphonyl-isocyanate, carbamic acid ester, thiolcarbamic acid ester, -urea, -semi-carbazide or -semicarbazone carrying the substituent



in the *p*-position with an amine carrying the substituent



or a salt thereof, reacting a sulphonamide of the formula



or a salt thereof with an isocyanate, carbamic acid ester, thiolcarbamic acid ester, carbamic acid halide or urea carrying the substituent



c) hydrolysing a correspondingly substituted benzenesulphonyl-isourea ether, -isourea ester, -isothiurea ether, -parabanic acid or -haloformic acid amidine, adding water on to a correspondingly substituted carbodiimide,

e) replacing the sulphur atom in a correspondingly substituted benzenesulphonyl-thiourea by an oxygen atom,

f) hydrogenating a corresponding benzenesulphonyl-urea containing, in the molecule, an unsaturated linkage, or

g) introducing by acylation the radical



into a benzenesulphonyl-urea of the formula



and, if desired, converting the resulting compound into a physiologically tolerable salt thereof by reaction with a base.

15. A process as claimed in claim 14, and conducted substantially as described in Example 1 or 4 herein.

16. A process as claimed in claim 14, and conducted substantially as described in any one of Examples 2, 3 and 5 to 30 herein.

17. A process for the manufacture of N-[4-(β -<2-methoxy-5-chloro-benzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea, conducted substantially as described in Example 4 herein.

18. A process for the manufacture of N-[4-(β -<2-methoxy-5-chloro-benzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl urea, conducted substantially as described in any one of Examples 2, 3, 5 to 28 and 30 herein.

19. A pharmaceutical preparation suitable for the treatment of diabetes mellitus, which comprises a compound as claimed in claim 1, in admixture or conjunction with a pharmaceutically suitable carrier.

20. A pharmaceutical preparation suitable for the treatment of diabetes mellitus, which comprises a physiologically tolerable salt as claimed in claim 2, in admixture or conjunction with a pharmaceutically suitable carrier.

21. A pharmaceutical preparation suitable for the treatment of diabetes mellitus, which comprises N-[4-(β -<2-methoxy-5-chloro-benzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea in admixture or conjunction with a pharmaceutically suitable carrier.

22. A pharmaceutical preparation suitable for the treatment of diabetes mellitus, which comprises a physiologically tolerable salt as claimed in claim 8, in admixture or conjunction with a pharmaceutically suitable carrier.

23. A pharmaceutical preparation suitable for the treatment of diabetes mellitus, which comprises the sodium salt claimed in claim 9, in admixture or conjunction with a pharmaceutically suitable carrier.

24. A pharmaceutical preparation suitable for the treatment of diabetes mellitus, which comprises the compound claimed in any one of claims 4 to 7, in admixture or conjunction with a pharmaceutically suitable carrier.

25. A pharmaceutical preparation suitable for the treatment of diabetes mellitus, which comprises a compound as claimed in claim 10 or 11, in admixture or conjunction with a pharmaceutically suitable carrier.

26. A pharmaceutical preparation suitable for the treatment of diabetes mellitus, which comprises a compound as claimed in claim 12, 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 13, in admixture or conjunction with a pharmaceutically suitable carrier

5 28. A pharmaceutical preparation as claimed in any one of claims 19 to 27, which is in a form suitable for oral administration.

29. A pharmaceutical preparation as claimed in any one of claims 19 to 28, which is in unit dosage form.

10 30. A pharmaceutical preparation as claimed in claim 28 or 29, which is in the form of a tablet or powder.

31. A pharmaceutical preparation as claimed in claim 29 or 30, which contains 0.5 to 100 milligrams of the active substance per dosage unit. 15

32. A pharmaceutical preparation as claimed in claim 31, which contains 2 to 10 milligrams of the active substance per dosage unit. 20

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