

L031038



PATENT SPECIFICATION

NO DRAWINGS

L031088

Date of Application and filing Complete Specification: Dec. 30, 1964.

No. 52840/64.

Application made in Germany (No. F42627 IVb/12o) on April 16, 1964.

Application made in Germany (No. F43641 Iwb/12°) on Aug. 1, 1964.

Application made in Luxemburg (No. 47450) on Nov. 26, 1964.

Complete Specification Published: May 25, 1966.

© Crown Copyright 1966.

Index at acceptance:—C2 C(1J1A3, 1J1B, 1J1C2, 1J1Z, 2D43B, 2D43F, 2D43J, 2D43L, 2D43S2, 2D43S3, 2D43S4, 2D43Z1)

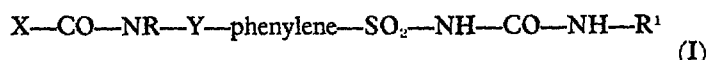
Int. Cl.:—C 07 c 143/78

COMPLETE SPECIFICATION

Benzenesulphonyl-Ureas and process for their manufacture

We, FARBWERKE HOECHST AKTIENGESSELLSCHAFT, vormals Meister Lucius & Brüning, a Company recognised by 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 provides benzenesulphonyl-ureas of the formula I



which, in the free form or in form of their physiologically tolerable salts, possess blood sugar lowering properties and which are distinguished by a strong and particularly long lasting lowering action on the blood sugar level.

In the above formula I

R is hydrogen, lower alkyl or phenyl lower alkyl,
R¹ is

- (a) alkyl, alkenyl or mercaptoalkyl of 2—8 carbon atoms,
- (b) alkoxyalkyl, alkylmercaptoalkyl or alkylsulfinylalkyl of 4-8 carbon atoms each, at least 2 of which carbon atoms forming the alkylene portion of the alkoxyalkyl, alkylmercaptoalkyl or alkylsulfinylalkyl.
- (c) phenyl lower alkyl, phenyl-cyclopropyl,
- (d) cyclohexyl lower alkyl, cycloheptylmethyl, cycloheptylethyl or cyclooctylmethyl,
- (e) endoalkylene-cyclohexyl, endoalkylene-cyclohexenyl, endoalkylene-cyclohexylmethyl or endoalkylenecyclohexenylmethyl of 1 or 2 endoalkylene carbon atoms each,
- (f) lower alkyl-cyclohexyl, lower alkoxy-cyclohexyl,
- (g) cycloalkyl of 5—8 carbon atoms each,
- (h) cyclohexenyl, cyclohexenylmethyl,
- (i) a heterocyclic nucleus of 4 or 5 carbon atoms, an oxygen or sulfur atom and up to 2 ethylenic double linkages and
- (k) the heterocyclic nucleus defined under (i) bound to the adjacent nitrogen atom via methylene,

X is

- (a) alkyl, alkenyl, alkoxyalkyl or alkylmercaptoalkyl of 4 to 11 carbon atoms,
- (b) cycloalkyl, cycloalkenyl, cycloalkyl-lower alkyl, cycloalkenyl-lower alkyl, lower cycloalkyl, or lower alkyl-cycloalkenyl of 4—8 ring carbon atoms,
- (c) endoalkylene-cyclohexyl or endoalkylene-cyclohexenyl of 1 or 2 endoalkylene-carbon atoms,
- (d) cycloalkoxyalkyl, cycloalkyl-mercaptoalkyl, cycloalkyl-alkoxyalkyl or cycloalkyl-alkyl-mercaptoalkyl of 4—11 carbon atoms,
- (e) alkyl, cycloalkyl or cycloalkylalkyl substituted by one or two substituents selected from chlorine and bromine atoms and cyano groups, and

Y is hydrocarbon of 1—4 carbon atoms.

[Price 4s. 6d.]



The present invention furthermore provides a process for the manufacture of the above-specified benzenesulfonyl-ureas of the formula I. These benzenesulfonyl-ureas can be prepared according to the following methods:

- 5 (a) Benzenesulfonyl isocyanates, benzenesulfonyl carbamic acid esters, benzenesulfonyl thiocarbamic acid esters, benzene sulphonyl carbamic acid halides, or benzenesulfonyl-ureas, which are substituted by the group $X-CO-NR-Y$, are reacted with R^1 -substituted amines or, if desired, with their salts.

(b) Benzene-sulfonamides of the formula



- 10 or, if desired, their salts, are reacted with R^1 -substituted isocyanates, carbamic acid esters, thiocarbamic acid esters, carbamic acid halides or ureas.

- (c) Benzenesulfonyl halides substituted by the group $X-CO-NR-Y$ are reacted with R^1 -substituted ureas, iso-urea ethers, isothiurea ethers or parabanic acids and the benzenesulfonyl-isourea ethers, benzenesulfonyl-isothiurea ethers or benzenesulfonyl-parabanic acids are hydrolysed.

(d) The sulfur atom in correspondingly substituted benzenesulfonyl-thiureas is replaced by an oxygen atom.

(e) Corresponding benzenesulfinyl ureas or benzenesulfinyl-ureas are oxidized.

- 20 (f) The radical $X-CO-$ is introduced by acylation into benzenesulfonyl ureas of the formula



If desired, the compounds thus obtained may be hydrogenated in case they contain an unsaturated group in the radical X.

- 25 The above-mentioned benzenesulfonyl-carbamic acid esters or benzenesulfonyl-thiocarbamic acid esters may contain a low molecular weight alkyl radical or a phenyl radical in the alcohol component. The same applies to the R^1 -substituted carbamic acid esters or the corresponding mono-thiocarbamic acid esters. Throughout the specification and claims, the terms "low molecular weight" and "lower" when applied to a radical indicate that such a radical contains at most 4 carbon atoms.

- 30 As carbamic acid halides, the chlorides are particularly suitable.

- The benzenesulfonyl-ureas to be used as starting substances in the process of the present invention may be unsubstituted at the side of the urea molecule opposite to the sulfonyl group or they may be substituted once or twice by lower alkyl or aryl radicals. Instead of benzenesulfonyl-ureas substituted in such manner, there may also be used corresponding N - benzenesulfonyl - N' - acylureas and bis - (benzenesulfonyl) - ureas. Such bis - (benzenesulfonyl) - ureas or N - benzenesulfonyl - N' - acylureas may, for example, be treated with amines R^1NH_2 and the salts obtained may then be heated to elevated temperatures, in particular to temperatures above 100°C.

- 40 Furthermore, it is possible to start from ureas of the formula



or from acylated ureas of the formula $R^1-NH-CO-NH-\text{acyl}$, wherein acyl represents preferably a low molecular weight aliphatic or aromatic acid radical or the nitro group, or from phenyl-ureas of the formula

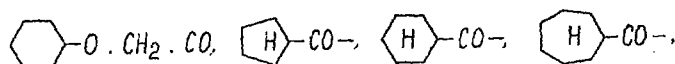
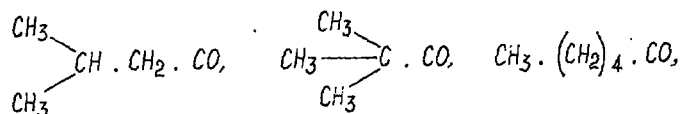
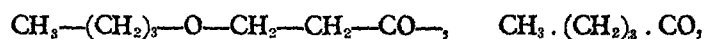
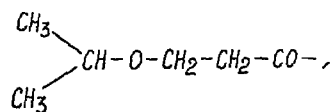
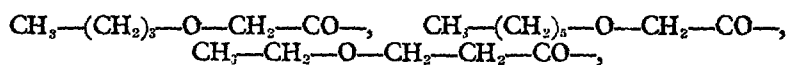
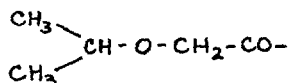
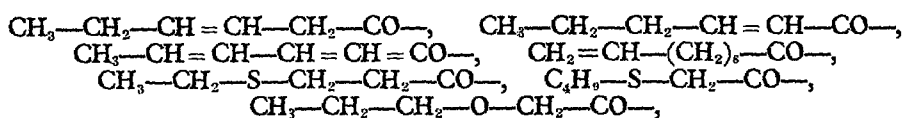
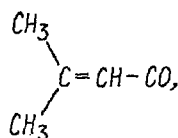
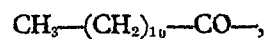
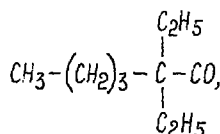
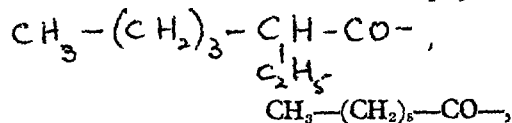
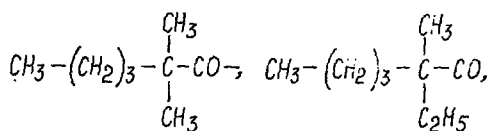
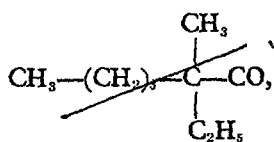
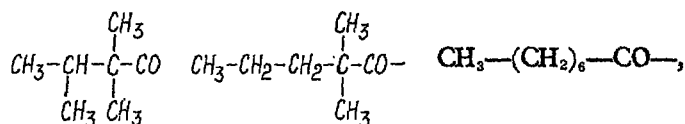


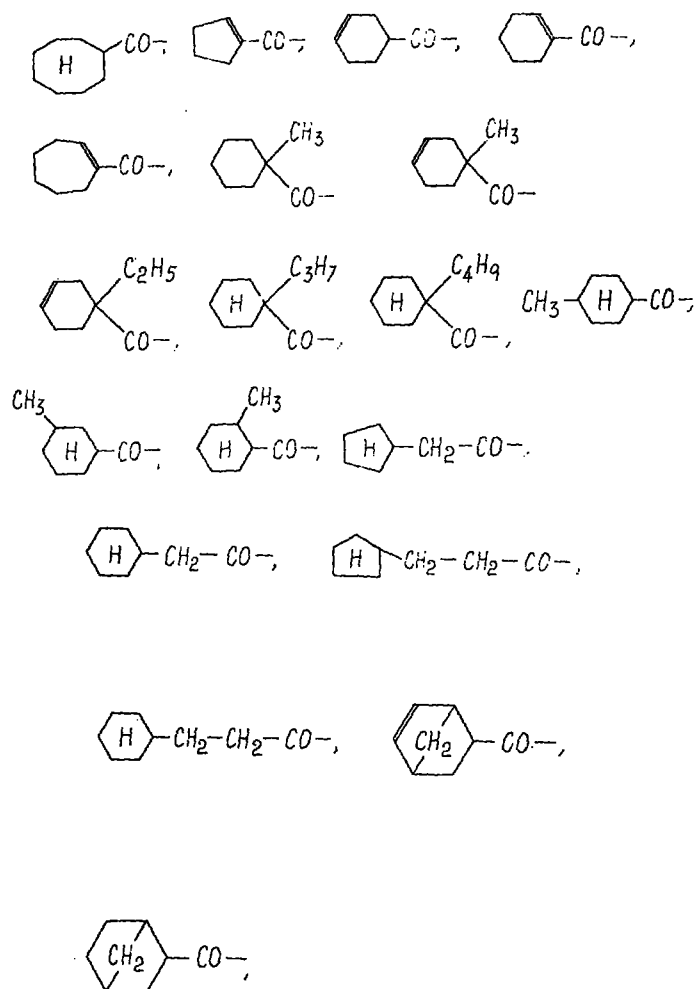
- or from diphenyl-ureas of the formula $R^1-NH-CO-N(C_6H_5)_2$, in which the phenyl radicals may be substituted and linked with one another either directly or through a bridging member such as $-CH_2-$, $-NH-$, $-O-$ or $-S-$, or from N,N-disubstituted ureas of the formula $R^1-NH-CO-NH-R^1$ and to react these with benzenesulfon-amides substituted by the grouping $X-CONH-Y-$.

50 The replacement of the sulfur atom in the correspondingly substituted benzene-sulfonyl-thiureas by an oxygen atom can be carried out, for example, with the aid of oxides or salts of heavy metals or even by application of oxidizing agents such as hydrogen peroxide, sodium peroxide or nitrous acid.

As regards the reaction conditions, the forms of realizing the process of the present invention may in general vary within wide limits and adapted to each individual case. For example, the reactions using solvents may be carried out at room temperature or at an elevated temperature.

As starting substances, there are used, on the one hand compounds which contain a benzene radical substituted by the group $X-\text{CONR}-Y$. As examples of the component $X-\text{CO}-$ of that formula, there may be mentioned the following groups:

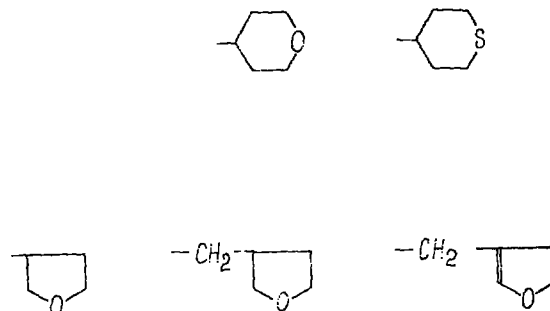




- In the above formulae, R' may represent, for example, ethyl, propyl, isopropyl, butyl, isobutyl, sec. butyl, straight chain or branched amyl (pentyl), hexyl, heptyl or octyl; radicals which correspond to the mentioned hydrocarbon radicals but contain an ethylenic double linkage, for example allyl or crotyl, furthermore such alkyl groups having 2—8 carbon atoms which, in addition, carry one mercapto group, for example, β - mercaptoethyl or higher mercaptoalkyls. Furthermore, R' may represent, for example, γ - methoxypropyl, δ - methoxy - n - butyl, β - ethoxyethyl, γ - ethoxypropyl, δ - ethoxybutyl or higher alkoxyethyl groups, alkoxypropyl groups or alkoxybutyl groups and the corresponding groups which carry a sulfur atom or the bridging member —SO— instead of the oxygen atom. Furthermore, there may be used as R' benzyl, α -phenylethyl, β -phenylethyl, α -phenylpropyl, β -phenylpropyl or γ -phenylpropyl or phenylbutyl groups.
- Particularly suitable for the process of the invention are such compounds as contain as R' a cycloaliphatic hydrocarbon radical which may be substituted by alkyl or alkoxy or which may be linked with the nitrogen atom via an alkylene radical. As such radicals, there may be mentioned, for example, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, methylcyclohexyl, ethylcyclohexyl, propylcyclohexyl, isopropylcyclohexyl, methoxycyclohexyl, ethoxycyclohexyl, propoxycyclohexyl, isopropoxycyclohexyl; in these radicals the alkyl or alkoxy groups may be in 2-, 3- or, preferably, 4-position, in both the cis- and the trans-position; furthermore, cyclohexylmethyl, α -cyclohexylethyl or β -cyclohexylethyl, cyclohexylpropyl radicals, endomethylene cyclohexyl - (2,2,1 - tricycloheptyl), endoethylenecyclohexyl - (2,2,2 - tricyclooctyl) endomethylenecyclohexenyl, endoethylenecyclohexenyl, endomethylenecyclohexylmethyl, endoethylenecyclohexylmethyl, endomethylenecyclohexenylmethyl or

endoethylenecyclohexenylmethyl, α - phenylcyclopropyl, or β - phenylcyclopropyl, both in cis- and trans-form.

Finally, there are also suitable as R' those heterocyclic rings which, in addition to 4—5 carbon atoms, carry 1 oxygen atom or sulfur atom and up to 2 double linkages and which may be bound to the adjacent nitrogen atom through a methylene group. Examples of such heterocyclic rings are, for example:



The phenylene radical, designated in the formula I by "phenylene", may be unsubstituted or substituted once or twice by halogen, lower alkyl or lower alkoxy. It may carry the other parts of the molecule in o-, m- or p-position to one another, the p-position being preferred.

The radical R in the formula I may represent, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert. butyl, benzyl, α - or β -phenylethyl, α -, β - or γ -phenylpropyl. Compounds in which R is methyl or benzyl and especially those in which R is hydrogen are preferred.

The blood sugar lowering action of the benzenesulfonyl urea derivatives described above was determined by measuring over a prolonged period of time, according to the known method of Hagedorn-Jensen or with an autoanalyzer the blood sugar level of rabbits which had been fed with the compounds in doses of 50 milligrams/kilogram (mg/kg).

Thus, it was found, for example, that N - [4 - (β - cyclopentanecarbonamidoethyl) - benzenesulfonyl] - N' - cyclohexyl urea provoked, after 6 hours, a lowering of the blood sugar level by 37%, whereas upon administration of the known N-(4-methyl-benzenesulfonyl)-N'-n-butyl-urea the blood sugar level was reduced by 30%.

In doses of 10 mg/kg, for example, N - [4 - (β - capronamidoethyl) - benzenesulfonyl] - N' - (4 - methylcyclohexyl) - urea lowers the blood sugar level, after 3 hours, by 33%, N - [4 - (β - trimethylacetamidoethyl) - benzenesulfonyl] - N' - (4 - methyl - cyclohexyl) - urea lowers the blood sugar level, after 3 hours, by 24%, and N - [4 - (β - trimethyl - acetamidoethyl) - benzenesulfonyl] - N' - cyclohexyl urea lowers the blood sugar level by 17%.

The strong blood sugar lowering action of the products of the present invention becomes particularly evident when reduced doses are administered. Thus, when N - [4 - (β - cyclopentanecarbonamidoethyl) - benzenesulfonyl] - N' - cyclohexyl urea or N - [4 - (β - cyclohexanecarbonamidoethyl) - benzenesulfonyl] - N' - (4 - methyl - cyclohexyl) - urea is administered in doses of 1 mg/kg to rabbits, a distinct lowering of the blood sugar level can still be observed, whereas the aforementioned N - (4 - methyl - benzenesulfonyl) - N' - n - butyl urea is no longer active when administered to rabbits in a dose of less than 25 mg/kg.

The products of the present invention are intended to be used preferably in the manufacture of orally administerable preparations that have blood sugar lowering action in the treatment of diabetes mellitus; they can be applied as such or in form of their physiologically tolerable salts or in the presence of substances that cause such salt formation. For such salt formation, there may be used, for example, alkaline agents such as alkali metal hydroxides, alkaline earth metal hydroxides, alkali metal carbonates and alkaline earth metal carbonates, alkali metal bicarbonates and alkaline earth metal bicarbonates. As pharmaceutical preparations, there enter into consideration preferably tablets which contain, in addition to the products of the invention, the usual adjuvants and carriers such as talc, starch, lactose, tragacanth or magnesium stearate.

A preparation containing the above-mentioned benzenesulfonyl ureas as the active substance, for example, a tablet or a powder, with or without the above-

mentioned additives, is suitably processed into a suitable unit dosage form. The dose chosen should comply with the efficacy of the benzenesulfonyl-urea used and with the desired effect. Advantageously, the dosage per unit is in the range of from 0.5 to 100 mg., preferably 2 to 10 mg. However, considerably higher or lower dosage units may also be used which, if desired, may be divided or multiplied prior to their application.

The following Examples illustrate the invention but they are not intended to limit it thereto:

EXAMPLE 1.

N-[4-(β -capronamido-ethyl)-benzenesulfonyl]-N'-(4-methyl-cyclohexyl)-urea

8.6 g of N - [4 - (β - capronamido - ethyl) - benzenesulfonyl] - urea (melting point 172—173°C.; obtained from 4 - (β - capronamido - ethyl) - benzenesulfonamide by the reaction with potassium cyanate) are heated for 5 hours under reflux, while stirring, together with 300 ml of toluene, 30 ml of glycolmonomethyl ether, 1.65 g of glacial acetic acid and 3.1 g of 4 - methylcyclohexylamine. The whole is then concentrated under reduced pressure and the residue is triturated with alcohol. The N - [4 - (β - capronamido - ethyl) - benzenesulfonyl] - N' - (4 - methylcyclohexyl)-urea obtained as crude product is filtered off with suction and recrystallized from methanol.

(Melting point: 181—182.5°C.).

In analogous manner there are obtained:

N-[4-(β -capronamido-ethyl)-benzenesulfonyl]-N'-cyclohexyl-urea, melting point 170—171°C. (from methanol); and

N - [4 - (β - capronamido - ethyl) - benzenesulfonyl] - N' - (4 - ethyl - cyclohexyl) - urea (trans), melting point 175—176°C. (from methanol).

EXAMPLE 2.

N-[4-(β -trimethylacetamido-ethyl)-benzenesulfonyl]-N'-cyclohexyl-urea

34.3 g of N - [4 - (β - trimethylacetamido - ethyl) - benzenesulfonyl] - methylurethane (melting point 189—191°C. (decomp.)); obtained by the reaction of 4-(β -trimethylacetamido-ethyl)-benzenesulfonamide with chloroformic acid methyl ester in the presence of potash are suspended in 50 ml of xylene and to this suspension are added dropwise, at 70°C. and while stirring, 10 g of cyclohexylamine. After termination of the dropwise addition, the temperature is raised to 120—130°C., the reaction setting in with evolution of methanol. After 30 minutes, the whole is allowed to cool, the N - [4 - (β - trimethylacetamido - ethyl) - benzenesulfonyl] - N' - cyclohexyl urea formed in good yield is filtered off with suction and recrystallized from methanol. (Melting point 184—186°C.).

In analogous manner, there are obtained:

N - [4 - (β - trimethylacetamido - ethyl) - benzenesulfonyl] - N' - cyclooctyl-urea, melting point 199°C. (from methanol);

N - [4 - (β - trimethylacetamido - ethyl) - benzenesulfonyl] - N' - (4 - methylcyclohexyl) - urea, melting point 177—178°C., (from methanol); and

N - [4 - (β - trimethylacetamido - ethyl) - benzenesulfonyl] - N' - (4 - ethylcyclohexyl) - urea (trans), melting point 116—118°C. (from methanol).

EXAMPLE 3.

N-[4-(β - β' -ethylmercapto-propionamido-ethyl)-benzenesulfonyl]-N'-(4-methyl-cyclohexyl)-urea (trans)

15.8 g of 4 - (β - β' - ethylmercapto - propionamido - ethyl) - benzenesulfonamide (melting point 136—137°C., obtained by the reaction of β - ethylmercapto - propionic acid chloride with 4 - β - aminoethyl - benzenesulfonamide) are dissolved in 25 ml of binormal sodium hydroxide solution and 50 ml of acetone, and to this solution are added dropwise, at 0—5°C., 7 g of 4 - methylcyclohexylisocyanate (trans). The whole is stirred for 3 hours, diluted with water and a small amount of methanol, undissolved matter is filtered off, and the filtrate is acidified with dilute hydrochloric acid. The N - [4 - (β - β' - ethylmercapto - propionamido-ethyl) - benzenesulfonyl] - N' - (4 - methylcyclohexyl) - urea (trans) which precipitates in very good yield melts at 144.5—146°C. (after recrystallization from methanol).

In analogous manner, there are obtained:

N - [4 - (β - β' - ethylmercapto - propionamido - ethyl) - benzenesulfonyl]-N' - cyclohexyl - urea, melting point 173—175°C. (from methanol); and



1 c

N - [4 - (β - β' - ethylmercapto - propionamido - ethyl) - benzenesulfonyl] - N' - (4 - ethylcyclohexyl - urea) (trans), melting point 163.5—165°C. (from methanol).

In analogous manner, there are obtained:

- | | | |
|----|---|----|
| 5 | from 4 - (β - isovaleramido - ethyl) - benzenesulfonamide (melting point 155°C.): | 5 |
| | N - [4 - (β - isovaleramido - ethyl) - benzenesulfonyl] - N' - (4 - methylcyclohexyl) - urea (trans), melting point 197—198.5°C. (from methanol); and | |
| | N - [4 - (β - isovaleramido - ethyl) - benzenesulfonyl] - N' - (4 - ethylcyclohexyl) - urea (trans), melting point 188.5—190°C. (from methanol); | |
| 10 | from 4-(β -diethylacetamido-ethyl)-benzenesulfonamide (melting point 170—171°C.): | 10 |
| | N - [4 - (β - diethylacetamido - ethyl) - benzenesulfonyl] - N' - cyclohexyl-urea, melting point 192—192.5°C. (from methanol); | |
| | N - [4 - (β - diethylacetamido - ethyl) - benzenesulfonyl] - N' - (4 - methylcyclohexyl)-urea (trans), melting point 205—206°C. (from methanol); and | |
| 15 | N - [4 - (β - diethylacetamido - ethyl) - benzenesulfonyl] - N' - (4 - ethylcyclohexyl)-urea (trans), melting point 198.5—199°C. (from methanol); | 15 |
| | from 4-(β -dimethylacrylamido-ethyl)-benzenesulfonamide (melting point 168°C.): | |
| | N - [4 - (β - dimethylacrylamido - ethyl) - benzenesulfonyl] - N' - cyclohexyl-urea, melting point 183—184°C. (from methanol); | |
| 20 | N - [4 - (β - dimethylacrylamido - ethyl) - benzenesulfonyl] - N' - (4 - methylcyclohexyl)-urea (trans), melting point 157—158°C. (from methanol); and | 20 |
| | N - [4 - (β - dimethylacrylamido - ethyl) - benzenesulfonyl] - N' - (4 - ethylcyclohexyl)-urea (trans), melting point 145—147°C. (from methanol); | |
| 25 | from 4-(β - α' - α' -dimethylvaleramido-ethyl)-benzenesulfonamide (melting point 127°C.): | 25 |
| | N - [4 - (β - α' - α' - dimethylvaleramido - ethyl) - benzenesulfonyl] - N' - cyclohexyl-urea, melting point 180—181.5°C. (from methanol); and | |
| | N - [4 - (β - α' - α' - dimethylvaleramido - ethyl) - benzenesulfonyl] - N' - (4-methylcyclohexyl)-urea (trans), melting point 194—196°C. (from methanol); | |
| 30 | from 4 - (β - isocapronamido - ethyl) - benzenesulfonamide (melting point 145°C.): | 30 |
| | N - [4 - (β - isocapronamido - ethyl) - benzenesulfonyl] - N' - cyclohexyl-urea, melting point 190—191°C. (from methanol); | |
| | N - [4 - (β - isocapronamido - ethyl) - benzenesulfonyl] - N' - (4 - methylcyclohexyl)-urea, (trans), melting point 198—200°C. (from methanol); and | |
| 35 | N - [4 - (β - isocapronamido - ethyl) - benzenesulfonyl] - N' - (4 - ethylcyclohexyl)-urea (trans), melting point 191—193°C. (from methanol); | 35 |
| | from 4-(β -n-octanamidoethyl)-benzenesulfonamide (melting point 146—148°C.): | |
| | N - [4 - (β - n - octanamido - ethyl) - benzenesulfonyl] - N' - cyclohexyl-urea, melting point 115—117°C. (from methanol); | |
| 40 | N - [4 - (β - n - octanamido - ethyl) - benzenesulfonyl] - N' - (4 - methylcyclohexyl)-urea (trans), melting point 166—168°C. (from methanol); | 40 |
| | N - [4 - (β - n - octanamido - ethyl) - benzenesulfonyl] - N' - (4 - ethylcyclohexyl)-urea (trans), melting point 161—164°C. (from methanol); | |
| | from 4-(β -n-decanamido-ethyl)-benzenesulfonamide (melting point 151—152°C.): | |
| 45 | N - [4 - (β - n - decanamido - ethyl) - benzenesulfonyl] - N' - cyclohexyl-urea, melting point 133—134°C. (from methanol); | 45 |
| | N - [4 - (β - n - decanamido - ethyl) - benzenesulfonyl] - N' - (4 - methylcyclohexyl)-urea (trans), melting point 169—171°C. (from methanol); and | |
| | N - [4 - (β - n - decanamido - ethyl) - benzenesulfonyl] - N' - (4 - ethylcyclohexyl)-urea (trans), melting point 158—160°C. (from methanol); | |
| 50 | from 4-(β - α' -methyl- α' -ethylcapronamido-ethyl)-benzenesulfonamide (melting point 123—124°C.): | 50 |
| | N - [4 - α' - methyl - α' - ethylcapronamido - ethyl) - benzenesulfonyl] - N' - cyclohexyl-urea, melting point 150—152°C. (from methanol); | |
| 55 | from 4-(β - β' -n-butoxypropionamido-ethyl)-benzenesulfonamide (melting point 72—75°C.): | 55 |
| | N - [4 - (β - β' - n - butoxypropionamido - ethyl) - benzenesulfonyl] - N' - cyclohexyl-urea, melting point 105—107°C. (from methanol); | |
| | N - [4 - (β - β' - n - butoxypropionamido - ethyl) - benzenesulfonyl] - N' - (4-methylcyclohexyl)-urea (trans), melting point 144—145°C. (from methanol); and | |
| 60 | N - [4 - (β - β' - n - butoxypropionamido - ethyl) - benzenesulfonyl] - N' - (4-ethylcyclohexyl)-urea (trans), melting point 142—143.5°C. (from methanol); | 60 |
| | from 4-(β - Δ^3 -tetrahydrobenzamido-ethyl)-benzenesulfonamide (melting point 198—200°C.): | |

- N - [4 - (β - Δ^3 - tetrahydro - benzamido - ethyl) - benzenesulfonyl] - N' - (4-ethylcyclohexyl)-urea (trans), melting point 193—194°C. (from methanol);
from 4-(β -cyclohexane-carbonamido-ethyl)-benzenesulfonamide (melting point 191—192°C.):
- 5 N - [4 - (β - cyclohexane - carbonamido - ethyl) - benzenesulfonyl] - N' - (4-ethylcyclohexyl)-urea (trans), melting point 198—199°C. (from methanol);
from 4-(β -capronamido-ethyl)-benzenesulfonamide (melting point 137—138°C.):
- 10 N - [4 - (β - capronamido - ethyl) - benzenesulfonyl] - N' - butyl-urea, melting point 126—127°C. (from methanol);
from 4-(β -trimethyl-acetamido-ethyl)-benzenesulfonamide (melting point 188—189°C.):
- 15 N - [4 - (β - trimethyl - acetamido - ethyl) - benzenesulfonyl] - N' - butyl-urea, melting point 185—187°C. (from methanol);
from 4-(β -diethyl-acetamido-ethyl)-benzenesulfonamide (melting point 170—171°C.):
- 20 N - [4 - (β - diethyl - acetamido - ethyl) - benzenesulfonyl] - N' - butyl - urea, melting point 169—170°C. (from methanol);
from 4 - (β - $\langle\beta$ - ethyl - mercapto - propionamido $\rangle$ - ethyl) - benzenesulfonamide (melting point 136—137°C.):
- 25 N' - [4 - (β - $\langle\beta$ - ethyl - mercapto - propionamido $\rangle$ - ethyl) - benzenesulfonyl] - N'-butyl-urea, melting point 118—120°C. (from methanol);
from 4 - (β - $\langle\alpha$ - methyl - α - ethyl - capronamido $\rangle$ - ethyl) - benzenesulfonamide (melting point 123—124°C.):
- 30 N - [4 - (β - $\langle\alpha$ - methyl - α - ethyl - capronamido $\rangle$ - ethyl) - benzenesulfonyl] - N'-butyl-urea, melting point 122—124°C. (from methanol);
N - [4 - (β - $\langle\alpha$ - methyl - α - ethyl - capronamido $\rangle$ - ethyl) - benzenesulfonyl] - N'-(4-methyl-cyclohexyl)-urea (trans), melting point 127—129°C. (from methanol);
N - [4 - (β - $\langle\alpha$ - methyl - α - ethyl - capronamido $\rangle$ - ethyl) - benzenesulfonyl] - N'-(4-ethyl-cyclohexyl)-urea (trans), melting point 129—131°C. (from methanol);
from 4-(β -hexene- $\langle 3 \rangle$ -amido-ethyl)-benzenesulfonamide (melting point 136—138°C.):
- 35 N - [4 - (β - hexene - $\langle 3 \rangle$ - amido - ethyl) - benzenesulfonyl] - N' - cyclohexyl-urea, melting point 164—165°C. (from methanol);
N - [4 - (β - hexene - $\langle 3 \rangle$ - amido - ethyl) - benzenesulfonyl] - N' - (4-methyl - cyclohexyl) - urea (trans), melting point 170—171°C. (from methanol);
and
- 40 N - [4 - (β - hexene - $\langle 3 \rangle$ - amido - ethyl) - benzenesulfonyl] - N' - (4 - ethyl-cyclohexyl)-urea (trans), melting point 162—163°C. (from methanol);
from 4-(4-undecene- $\langle 10 \rangle$ -amido-ethyl)-benzenesulfonamide (melting point 139—140°C.):
- 45 N - [4 - (β - undecene - $\langle 10 \rangle$ - amido - ethyl) - benzenesulfonyl] - N' - cyclohexyl-urea, melting point 128—130°C. (from methanol);
N - [4 - (β - undecene - $\langle 10 \rangle$ - amido - ethyl) - benzenesulfonyl] - N' - 4-(methyl-cyclohexyl)-urea (trans), melting point 163.5—165°C. (from methanol);
and
- 50 N - [4 - (β - undecene - $\langle 10 \rangle$ - amido - ethyl) - benzenesulfonyl] - N' - 4-(ethyl-cyclohexyl)-urea (trans), melting point 154—155°C. (from methanol);
from 4-(β -dodecane-amido-ethyl)-benzenesulfonamide (melting point 152—154°C.):
- 55 N - [4 - (β - dodecane - amido - ethyl) - benzenesulfonyl] - N' - cyclohexyl-urea, melting point 132—134°C. (from dimethylformamide/water);
N - [4 - (β - dodecane - amido - ethyl) - benzenesulfonyl] - N' - (4 - methyl-cyclohexyl)-urea (trans), melting point 171—173°C. (from dimethylformamide/water);
N - [4 - (β - dodecane - amido - ethyl) - benzenesulfonyl] - N' - (4 - ethyl-cyclohexyl)-urea (trans), melting point 162—164°C. (from dimethylformamide/water);
- 60 from 4-(capronamido-methyl)-benzenesulfonamide (melting point 183—184°C.):
N - [4 - (capronamido - methyl) - benzenesulfonyl] - N' - cyclohexyl - urea, melting point 167—168°C. (from methanol);
N - [4 - (capronamido - methyl) - benzenesulfonyl] - N' - (4 - methylcyclohexyl)-urea (trans), melting point 184—185°C. (from methanol); and
N - [4 - (capronamido - ethyl) - benzenesulfonyl] - N' - (4 - ethylcyclohexyl)-urea (trans), melting point 183.5—185°C. (from methanol).

EXAMPLE 4.

N-[4-(β -hexadiene-(2,4)-amido-(1)-ethyl-benzenesulfonyl]-N'-cyclohexyl-urea
13.1 g of 4 - (β - hexadiene - (2,4) - amido - (1) - ethyl) - benzenesulfonamide

- (melting point 208—210°C., prepared from 4 - aminoethyl - benzenesulfonamide and hexadiene - (2,4) - acid chloride) are dissolved in 200 ml of acetone with 2 g of sodium hydroxide and water. To this solution are added dropwise, while stirring, at room temperature 6.5 g of cyclohexylisocyanate and the whole is further stirred for 2 hours. The reaction solution is filtered, combined with water and acidified. The product is filtered off with suction, dissolved and reprecipitated in ammonia having a strength of 1% and then dissolved and recrystallized in a mixture of ethanol and water. The N - [4 - (β - hexadiene - (2,4) - amido - (1) - ethyl) - benzenesulfonyl] - N'-cyclohexyl-urea thus obtained melts at 198—200°C.
- 5 In analogous manner, there are obtained:
- 10 N - [4 - (β - hexadiene - (2,4) - amido - (1) - ethyl) - benzenesulfonyl] - N'-butyl-urea, melting point 186—188°C.;
- N - [4 - β - hexadiene - (2,4) - amido - (1) - ethyl) - benzenesulfonyl] - N'-(4-methyl-cyclohexyl)-urea, melting point 203—205°C.;
- 15 N - [4 - (β - hexadiene - (2,4) - amido - (1) - ethyl) - benzenesulfonyl] - N'-(4-ethyl-cyclohexyl)-urea, melting point 204—206°C.
- In analogous manner, there are obtained:
- from 4-(β-hexadiene-(2,4)-amido-(1)-methyl)-benzenesulfonamide (melting point 198—200°C.):
- 20 N - [4 - (β - hexadiene - (2,4) - amido - (1) - methyl) - benzenesulfonyl] - N'-cyclohexyl-urea, melting point 185—187°C.;
- N - [4 - (β - hexadiene - (2,4) - amido - (1) - methyl) - benzenesulfonyl] - N'-butyl-urea, melting point 194—195°C.
- In analogous manner, there are obtained:
- 25 from 4 - (β - hexadiene - (2,4) - amido - (1) - propyl) - benzenesulfonamide (melting point 149—151°C.):
- N - [4 - (hexadiene - (2,4) - amido - (1) - propyl) - benzenesulfonyl] - N'-cyclohexyl - urea, melting point 189—191°C.;
- from N-4-(γ-capronamidopropyl)-benzenesulfonamide (melting point 101°C.):
- 30 N - [4 - (γ - capronamidopropyl - benzenesulfonyl] - N' - (4 - methylcyclohexyl)-urea, melting point 192°C. (from methanol/water);
- from N-4-(β-capronamidopropyl)-benzenesulfonamide (melting point 104°C.):
- N - [4 - (β - capronamidopropyl) - benzenesulfonyl] - N' - cyclohexyl - urea, melting point 171°C. (from methanol/water);
- 35 N - [4 - (β - capronamidopropyl) - benzenesulfonyl] - N' - (4 - methyl - cyclohexyl)-urea, melting point 144°C.;
- from 4 - (β - dimethyl - isopropyl - acetamidoethyl) - benzenesulfonamide (melting point 179—181°C.):
- 40 N - [4 - (β - dimethyl - isopropyl - acetamido - ethyl) - benzenesulfonyl] - N'-cyclohexyl-urea, melting point 193—195°C.;
- N - [4 - (β - dimethyl - isopropyl - acetamido - ethyl) - benzenesulfonyl] - N'-(4-methyl-cyclohexyl)-urea, melting point 182—184°C.;
- N - [4 - (β - dimethyl - isopropyl - acetamido - ethyl) - benzenesulfonyl] - N'-butyl-urea, melting point 175—177°C.;
- 45 from 4 - (β - 2,2 - diethyl - capronamidoethyl) - benzenesulfonamide (melting point 147—149°C.):
- N - [4 - β - 2,2 - diethyl - capronamido - ethyl) - benzenesulfonyl] - N' - cyclohexyl-urea, melting point 171—173°C.;
- N - [4 - (β - 2,2 - diethyl - capronamido - ethyl) - benzenesulfonyl] - N' - (4-methyl-cyclohexyl)-urea, melting point 157—159°C.;
- 50 N - [4 - (β - 2,2 - diethyl - capronamido - ethyl) - benzenesulfonyl] - N'-butyl-urea, melting point 132—134°C.;
- from 4 - (β - 2,4 - dimethyl - valeramido - ethyl) - benzenesulfonamide (melting point 141—143°C.):
- 55 N - [4 - (β - 2,4 - dimethyl - valeramido - ethyl) - benzenesulfonyl] - N'-cyclohexyl-urea, melting point 200—202°C.;
- N - [4 - (β - 2,4 - dimethyl - valeramido - ethyl) - benzenesulfonyl] - N'-(4-methyl-cyclohexyl)-urea, melting point 209—210°C.;
- N - [4 - (β - 2,4 - dimethyl - valeramido - ethyl) - benzenesulfonyl] - N'-butyl-urea, melting point 142—144°C.
- 60

EXAMPLE 5.

N-[4-(hexahydrobenzamidomethyl)-benzenesulfonyl]-N'-cyclohexyl-urea
29.4 g of 4-(hexahydrobenzamidomethyl)-benzenesulfonamide are suspended in

250 ml of acetone. To this suspension, there are added an aqueous solution of 4 g of sodium hydroxide and then water, until a clear solution is formed. 12.5 g of cyclohexylisocyanate are added dropwise, while stirring, at room temperature, whereupon a thick precipitate is formed slowly. The whole is stirred for 2 hours, combined with hydrochloric acid and water and then filtered with suction. The N-[4-hexahydrobenzamido-methyl]-benzenesulfonyl]-N'-cyclohexyl-urea thus obtained melts at 192°C. (after recrystallization from ethanol).

In analogous manner, there is obtained the

N-[4-(hexahydrobenzamidomethyl)-benzenesulfonyl]-N'-butyl-urea, melting at 186—188°C.

EXAMPLE 6.

N-[4-(β -endomethylene-2',5'- Δ^3 -tetrahydrobenzamidoethyl)-benzenesulfonyl]-N'-cyclohexyl-urea

16 g of 4-(β -endomethylene-2',5'- Δ^3 -tetrahydrobenzamidoethyl)-benzenesulfonamide (melting point 149—151°C., prepared from 4-(aminoethyl)-benzenesulfonamide and endomethylene-2,5- Δ^3 -tetrahydrobenzoyl chloride) are suspended in 200 ml of acetone. To this suspension, there is added a solution of 2 g of sodium hydroxide in a small amount of water and then so much water until a clear solution is formed. To this solution, 6.5 g of cyclohexyl isocyanate are added dropwise at room temperature, while stirring, and stirring is continued for 2 hours. The reaction mixture is filtered and combined with water and hydrochloric acid. The product is filtered off with suction and recrystallized from a mixture of ethanol and water. The

N-[4-(β -endomethylene-2',5'- Δ^3 -tetrahydrobenzamido-ethyl)-benzenesulfonyl]-N'-cyclohexyl-urea melts at 194—196°C.

In analogous manner, there is obtained:

from 4-(endomethylene-2,5- Δ^3 -tetrahydrobenzamido-methyl)-benzenesulfonamide (melting point 159—161°C.) and cyclohexyl isocyanate:

N-[4-(endomethylene-2',5'- Δ^3 -tetrahydrobenzamido-methyl)-benzenesulfonyl]-N'-cyclohexyl-urea, melting point 171—173°C.;

from 4-(β -endomethylene-2',5'-hexahydrobenzamido-ethyl)-benzenesulfonamide (melting point 149—151°C.) and cyclohexyl isocyanate:

N-[4-(β -endomethylene-2',5'-hexahydrobenzamido-ethyl)-benzenesulfonyl]-N'-cyclohexyl-urea, melting point 208—210°C.

EXAMPLE 7.

N-[4-(β -cyclopentane-carbamido-ethyl)-benzenesulfonyl]-N'-cyclohexyl-urea

12 g of 4-(β -cyclopentane-carbamidoethyl)-benzenesulfonamide (melting point 162—164°C.) are dissolved in 20.5 ml of binormal sodium hydroxide solution and 50 ml of acetone; to this solution, there are added dropwise, at 0—5°C., 5.2 g of cyclohexyl isocyanate. The whole is stirred for 3 hours, diluted with 100 ml of water and 50 ml of methanol, undissolved matter is filtered off and the filtrate is acidified with dilute hydrochloric acid. The precipitated product is filtered off with suction and recrystallized from methanol. The N-[4-(β -cyclopentane-carbamido-ethyl)-benzenesulfonyl]-N'-cyclohexyl-urea melts at 214—215°C.

In analogous manner, there are obtained:

N-[4-(β -cyclopentane-carbamido-ethyl)-benzenesulfonyl]-N'-cyclo-octyl-urea, melting point 202—203°C. (from dimethylformamide/water);

N-[4-(β -cyclopentane-carbamido-ethyl)-benzenesulfonyl]-N'-butyl-urea, melting point 184—185°C. (from methanol);

N-[4-(β -cyclopentane-carbamido-ethyl)-benzenesulfonyl]-N'-(4-methyl-cyclohexyl)-urea, melting point 201—202°C. (from methanol);

N-[4-(β -cyclohexane-carbamido-ethyl)-benzenesulfonyl]-N'-cyclo-octyl-urea, melting point 205—206°C. (from methanol/dimethylformamide);

N-[4-(β -cyclohexane-carbamido-ethyl)-benzenesulfonyl]-N'-cyclohexyl-urea, melting point 195—196°C. (from methanol/dimethylformamide);

N-[4-(β -cyclohexane-carbamido-ethyl)-benzenesulfonyl]-N'-butyl-urea, melting point 156—157°C. (from methanol);

N-[4-(β -cyclohexane-carbamido-ethyl)-benzenesulfonyl]-N'-(4-

methyl-cyclohexyl)-urea, melting point 197—198°C. (from dimethylformamide/water);

N - [4 - (β - Δ^3 - tetrahydro - benzamido - ethyl) - benzenesulfonyl] - N'-cyclooctyl-urea, melting point 208—209°C. (from dimethylformamide/water);

5 N - [4 - (β - Δ^3 - tetrahydro - benzamido - ethyl) - benzenesulfonyl] - N'-cyclohexyl-urea, melting point 211—212°C. (from methanol); 5

N - [4 - (β - Δ^3 - tetrahydro - benzamido - ethyl) - benzenesulfonyl] - N'-butyl-urea, melting point 171—172°C. (from methanol);

10 N - [4 - (β - Δ^3 - tetrahydro - benzamido - ethyl) - benzenesulfonyl] - N'-(4 - methyl - cyclohexyl) - urea, melting point 198—200°C. (from dimethylformamide/water). 10

EXAMPLE 8.

N-[4-(β -cyclopentane-carbamido-ethyl)-benzenesulfonyl]-N'-(4-ethyl-cyclohexyl)-urea

15 To 17.7 g of N - [4 - (β - cyclopentane - carbamido - ethyl) - benzenesulfonyl] - methylurethane (melting point 118—120°C.) in 100 ml of toluene, there are added, while stirring, 6.3 g of 4-ethyl-cyclohexylamine. The temperature is raised to 120—130°C., whereupon the reaction sets in with evolution of methanol. After 30 minutes, the whole is allowed to cool, the precipitated urea is filtered off with suction, washed with benzene and recrystallized from a mixture of dimethylformamide and water. The N - [4 - (β - cyclopentane - carbamido - ethyl) - benzenesulfonyl] - N'-(4-ethyl-cyclohexyl)-urea melts at 187—188°C. 15 20

In analogous manner, there is obtained:

25 N - [4 - (β - cyclopentane - carbamido - ethyl) - benzenesulfonyl] - N' - (4-methoxy-cyclohexyl)-urea, melting point 200—201°C. (from dimethylformamide/water). 25

EXAMPLE 9.

N-[4-(β -1'-methyl- Δ^3 -tetrahydro-benzamido-ethyl)-benzenesulfonyl]-N'-cyclohexyl-urea

30 A mixture of 9.1 g of N - [4 - (β - 1' - methyl - Δ^3 - tetrahydro - benzamido - ethyl) - benzenesulfonyl] - urea (melting point 178°C.), 300 ml of toluene, 30 ml of glycol monomethyl ether, 165 g of glacial acid and 2.8 g of cyclohexylamine is heated for 5 hours under reflux, while stirring. The mixture is concentrated under reduced pressure, the residue is triturated with alcohol. The N - [4 - (β - 1' - methyl- Δ^3 - tetrahydro - benzamido - ethyl) - benzenesulfonyl] - N' - cyclohexyl - urea obtained as crude product is filtered off with suction and dissolved in and allowed to crystallize from a mixture of dimethylformamide and water. Melting point 210—211°C. 30 35

In analogous manner, there are obtained:

40 N - [4 - (β - 1' - Δ^3 - tetrahydro - benzamido - ethyl) - benzenesulfonyl] - N'-butyl-urea, melting point 166—167°C. (from dimethylformamide/water); 40

N - [4 - (β - 1' - Δ^3 - tetrahydro - benzamido - ethyl) - benzenesulfonyl] - N'-(4-methyl-cyclohexyl)-urea, melting point 193—195°C. (from methanol).

EXAMPLE 10.

45 N-[4-(β -1'-isobutyl-hexahydro-benzamido-ethyl)-benzenesulfonyl]-N'-cyclohexyl-urea 45

14 g of 4 - (β - 1' - isobutyl - hexahydro - benzamido - ethyl) - benzenesulfonylurea are dissolved in 100 ml of acetone and 100 ml of aqueous sodium hydroxide solution containing 1.5 g of NaOH. Then, 5 g of cyclohexyl-isocyanate are added dropwise at room temperature and the whole is stirred for 1 hour at room temperature. After the addition of water, the whole is filtered with charcoal. By acidification, there is first obtained a smeary precipitate which is dissolved in a sodium hydroxide solution having a strength of about 1%. Upon acidification with dilute hydrochloric acid, there is obtained a crystalline precipitate of N - [4 - (β - 1' - 50

isobutyl - hexahydro - benzamido - ethyl) - benzenesulfonyl] - N' - cyclohexyl-urea which, after dissolution in ammonia and precipitation with HCl, filtration and drying and following recrystallization from methanol, melts at 164—166°C.

EXAMPLE 11.

5 N-[4-(β -cyclopentane-2-yl-carbamido-ethyl)-benzenesulfonyl]-N'-cyclohexyl-urea 5

10 13.2 g of N - 4 - (β - cyclopentene - 2 - yl - carbonamido - ethyl) - benzene-sulfonamide are suspended in 200 ml of acetone. 12.5 g of ground potassium carbonate are added to this suspension, while stirring, and the whole is heated for 1½ hours under reflux, while continuously stirring. 5.6 g of cyclohexyl isocyanate are then added dropwise, while stirring and heating. The whole is further stirred and heated under reflux for 7 hours, the diluant is removed by distillation, the residue is dissolved in water, the solution is filtered and acidified. The N - [4 - (β - cyclopentene - 2 - yl - carbamido - ethyl) - benzenesulfonyl] - N' - cyclohexyl - urea obtained as the precipitate is filtered off with suction, dried and recrystallized from methanol. The substance melts at 198—200°C. 15

EXAMPLE 12.

20 N-[4-(β -hexahydro-benzamido-ethyl)-benzenesulfonyl]-N'-cyclohexyl-urea
9 g of N - [4 - (β - hexahydro - benzamido - ethyl) - benzenesulfonyl] - N'-cyclohexyl - thiourea (prepared by the reaction of N - 4 - (β - hexahydro - benzamido - ethyl) - benzenesulfonamide with cyclohexyl mustard oil in the presence of potassium carbonate and acetone; melting point after recrystallization from methanol: 127—129°C. are dissolved in excess amount of N - sodium hydroxide solution, and an excess amount of hydrogen peroxide having a strength of 3% is added to the solution. The solution is shortly heated on the steam bath. After cooling, the precipitated sulfur is filtered off, the solution is clarified with charcoal and the filtrate is acidified with dilute hydrochloric acid. The N - [4 - (β - hexahydro - benzamido - ethyl)-benzenesulfonyl] - N' - cyclohexyl - urea obtained in good yield melts, after recrystallization from a mixture of methanol and dimethylformamide, at 195—196°C. 25

EXAMPLE 13.

30 N-[4-(β -hexahydro-benzamido-ethyl)-benzenesulfonyl]-N'-cyclohexyl-urea
4.5 g of N - [4 - (hexahydro - benzamido - ethyl) - benzenesulfonyl] - N'-cyclohexyl - isourea methyl ether (prepared by the reaction of N - [4 - (β - hexahydro-benzamido - ethyl) - benzenesulfonyl] - N' - cyclohexyl - thiourea with mercury oxide in methanol; melting point 120—122°C., after recrystallization from ethyl acetate) in 100 ml of concentrated hydrochloric acid are heated for 5 minutes on the steam bath. The precipitated N - [4 - (β - hexahydro - benzamido - ethyl) - benzenesulfonyl] - N' - cyclohexyl - urea is filtered off with suction, triturated with water and recrystallized from a mixture of methanol and dimethylformamide. Melting point 195—196°C. 35 40

EXAMPLE 14.

45 N-[4-(β -cycloheptane-carbamido-ethyl)-benzenesulfonyl]-N'-cyclohexyl-urea
15 g of cycloheptane-carbamido-ethyl-benzenesulfonamide (melting point 181°C.; obtained from 4 - aminoethyl - benzenesulfonamide and cycloheptane - carboxylic acid chloride) are dissolved in 100 ml of acetone and 23 ml of binormal sodium hydroxide solution; to this solution, there are added dropwise, at 0—5°C., while stirring, 6.5 g of cyclohexyl isocyanate. The whole is stirred for 3 hours and then allowed to reach room temperature. The mixture is then acidified, acetone is removed under reduced pressure at room temperature and the residue is recrystallized from a mixture of ethanol and water. Melting point: 186°C. 50

In analogous manner, there are obtained:

55 N - [4 - (β - cycloheptane - carbamido - ethyl) - benzenesulfonyl] - N' - (4-methylcyclohexyl)-urea, melting point 201°C. (from ethanol);
N - [4 - (β - cycloheptene - (1) - carbamido - ethyl) - benzenesulfonyl] - N'-cyclohexyl-urea, melting point 177°C. (from ethanol); 55
N - [4 - (β - cycloheptene - (1) - carbamido - ethyl) - benzenesulfonyl] - N'-(4-methyl-cyclohexyl)-urea, melting point 165°C. (from methanol);
N - [4 - (β - cycloheptene - (1) - carbamido - ethyl) - benzenesulfonyl] - N'-n-butyl-urea, melting point 100°C. (from ethanol/water);
60 N - [4 - (β - cyclohexane - carbamido - propyl) - benzenesulfonyl] - N'-cyclohexyl-urea, melting point 177°C. (from ethanol/water); 60

N - [4 - (β - cyclohexene - (3) - carbamido - propyl) - benzenesulfonyl] - N' - cyclohexyl-urea, melting point 206°C. (from ethanol);

N - [4 - (γ - cyclohexane - carbamido - propyl) - benzenesulfonyl] - N' - cyclohexyl-urea, melting point 187°C. (from ethanol);

5 N - [4 - (γ - cyclohexane - carbamido - propyl) - benzenesulfonyl] - N' - n-butyl-urea, melting point 124°C. (from ethanol/water); 5

N - [4 - (γ - cyclohexene - (3) - carbamido - propyl) - benzenesulfonyl] - N' - cyclohexyl-urea, melting point 188°C. (from ethanol).

EXAMPLE 15.

10 N - [4 - (γ - cyclohexene - (3) - carbamido - propyl) - benzenesulfonyl] - N' - (4 - methyl - cyclohexyl) - urea 10

6.3 g of N - [4 - (γ - cyclohexene - (3) - carbamido) - propyl] - benzenesulfonamide sodium (prepared from 4 - (ω - aminopropyl) - benzenesulfonamide and cyclohexene - (3) - carboxylic acid chloride) together with 11 g of N,N - diphenyl - N' - (4 - methyl - cyclohexyl) - urea in 20 ml of dimethylformamide are kept for 7 15 hours at 100°C. After cooling and addition of water and binormal sodium hydroxide solution, the diphenylamine that has formed is shaken out with ether, the aqueous phase is treated with charcoal and acidified. The precipitate that has formed is directly recrystallized from ethanol and a small amount of water. Melting point 192°C. 20

EXAMPLE 16.

N - [4 - (β - cyclohexyl - propionamido - ethyl) - benzenesulfonyl] - N' - cyclohexyl-urea

25 10.1 g of 4 - (β - cyclohexyl - propionamido - ethyl) - benzenesulfonamide (melting point 147—149°C.) are suspended in 15 ml of binormal sodium hydroxide solution and 75 ml of acetone; to this suspension, 4.2 g of cyclohexyl isocyanate are added dropwise at 0—5°C. The whole is then stirred for 3 hours, diluted with water and methanol, undissolved matter is filtered off and the filtrate is acidified. The crystals of N - [4 - (β - cyclohexyl - propionamido - ethyl) - benzenesulfonyl] - N' - cyclohexyl-urea melt at 177—179°C. (after single recrystallization from methanol). 30

In analogous manner, there are obtained:

N - [4 - (β - cyclohexyl - propionamido - ethyl) - benzenesulfonyl] - N' - butyl-urea, melting point 154—155°C. (from methanol);

35 N - [4 - (β - cyclohexyl - acetamido - ethyl) - benzenesulfonyl] - N' - cyclohexyl-urea, melting point 183—184°C. (from methanol); 35

N - [4 - (β - cyclohexyl - acetamido - ethyl) - benzenesulfonyl] - N' - (4 - methyl - cyclohexyl) - urea, melting point 209—210°C. (from dimethylformamide/water).

In analogous manner, there is obtained:

40 from 4 - (β - cyclopentyl - propionamido - ethyl) - benzenesulfonamide (melting point 157°C.) and cyclohexyl isocyanate: 40

N - [4 - (β - cyclopentyl - propionamido - ethyl) - N' - cyclohexyl - urea, melting point 181°C.

EXAMPLE 17.

45 N - [2 - (β - cyclopentane - carbamido - ethyl) - 4 - chlorobenzenesulfonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans) 45

12 g of 2 - (β - cyclopentane - carbonamido - ethyl) - 4 - chloro - benzenesulfonamide (melting point 210°C.) are suspended in 18.5 ml of binormal sodium hydroxide solution and 60 ml of acetone, and 5.5 g of 4 - methylcyclohexylisocyanate (trans), are added dropwise, at 0—5°C., to this suspension. The reaction mixture is stirred for 3 hours, diluted with water, undissolved matter is filtered off and the filtrate is acidified with dilute hydrochloric acid. The N - [2 - (β - cyclopentane - carbonamido - ethyl) - 4 - chlorobenzenesulfonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans) obtained upon recrystallization from methanol melts at 178—180°C. 50

55 In similar manner, there are obtained: 55
from 4 - (β - $\langle$ N - methyl - capronamido $\rangle$ - ethyl) - benzenesulfonamide (melting point 135—137°C.):

60 N - [4 - (β - $\langle$ N - methyl - capronamido $\rangle$ - ethyl) - benzenesulfonyl] - N' - cyclohexyl-urea, melting point 90—92°C. (from methanol); and 60

N - [4 - (β - $\langle$ N - methyl - capronamido $\rangle$ - ethyl) - benzenesulfonyl] - N' - (4 - methylcyclohexyl) - urea (trans), melting point 80—83°C. (from methanol);

- from 4 - (β - 3 - cyclohexyloxy - propionamido - ethyl) - benzenesulfonamide (melting point 122—124°C.):
- N - [4 - (β - 3 - cyclohexyloxy - propionamido - ethyl) - benzenesulfonyl] - N' - cyclohexyl-urea, melting point 128—132°C.;
- 5 N - [4 - (β - 3 - cyclohexyloxy - propionamido - ethyl) - benzenesulfonyl] - N' - (4-methyl-cyclohexyl)-urea, melting point 145—147°C.; and
- N - [4 - (β - 3 - cyclohexyloxy - propionamido - ethyl) - benzenesulfonyl] - N' - butyl-urea, melting point 112—115°C.;
- 10 from 4 - (β - cyclohexyloxy - acetamido - ethyl) - benzenesulfonamide (melting point 162—164°C.):
- N - [4 - (β - cyclohexyloxy - acetamido - ethyl) - benzenesulfonyl] - N' - (4-ethyl-cyclohexyl)-urea, melting point 178—180°C.
- In analogous manner, there are obtained:
- 15 from 4 - (β - 2 - ethyl - capronamido - ethyl) - benzenesulfonamide (melting point 154—156°C.):
- N - [4 - (β - 2 - ethyl - capronamido - ethyl) - sulfonyl] - N' - 4' - methyl-cyclohexyl-urea, melting point 196—198°C.;
- from 4-(β -2-ethyl-capronamido-ethyl)-benzenesulfonamide:
- 20 N - [4 - (β - 2 - ethyl - capronamido - ethyl) - benzenesulfonyl] - N' - n - butyl-urea, melting point 151—152.5°C.;
- from 4-(β -2-ethyl-capronamido-ethyl)-benzenesulfonamide:
- N - [4 - (β - 2 - ethyl - capronamido - ethyl) - benzenesulfonyl] - N' - cyclohexyl-urea, melting point 151—153°C.;
- 25 from 4-(γ -2-ethyl-capronamido-propyl)-benzenesulfonamide:
- N - [4 - (γ - 2 - ethyl - capronamido - propyl) - benzenesulfonyl] - N' - cyclohexyl-urea, melting point 158—160°C.;
- from 4-(γ -2-ethyl-capronamido-propyl)-benzenesulfonamide:
- N - [4 - (γ - 2 - ethyl - capronamido - propyl) - benzenesulfonyl] - N' - 4' - methyl-cyclohexyl-urea, melting point 178—180°C.;
- 30 According to the isocyanate method, there are obtained:
- from 4 - (β - tetrahydro - cinnamoyl - amido - ethyl) - benzenesulfonamide (melting point 170—172°C.):
- N - [4 - (β - tetrahydro - cinnamoyl - amido - ethyl) - benzenesulfonyl] - N' - cyclohexyl-urea, melting point 192—194°C.;
- 35 from 4-(β -tetrahydro-cinnamoyl-amido-ethyl)-benzenesulfonamide:
- N - [4 - (β - tetrahydro - cinnamoyl - amido - ethyl) - benzenesulfonyl] - N' - 4-methyl-cyclohexyl-urea, melting point 213—215°C.;
- from 4-(β -tetrahydro-cinnamoylamido-ethyl)-benzenesulfonamide:
- 40 N - [4 - (β - tetrahydro - cinnamoylamido - ethyl) - benzenesulfonyl] - N' - n-butyl-urea, melting point 177—179°C.

EXAMPLE 18.

N - [4-(β -diethyl-cyanacetamido-ethyl)-benzenesulfonyl] - N' - (4-methyl-cyclohexyl)-urea (trans)

- 45 12 g of 4 - (β - diethyl - cyanacetamido - ethyl) - benzenesulfonamide (melting point 129—130°C.) are dissolved in 18.5 ml of binormal sodium hydroxide solution and 50 ml of acetone; to this solution, there are added dropwise, at 0—5°C., 5.3 g of 4 - methyl - cyclohexyl - isocyanate (trans). After having stirred for 3 hours at room temperature, the mixture is diluted with water, undissolved matter is filtered off and the filtrate is acidified with dilute hydrochloric acid. The N - [4 - (β -diethyl - cyanacetamido - ethyl) - benzenesulfonyl] - N' - (4 - methyl - cyclohexyl)-urea, obtained in the form of crystals, is then recrystallized from methanol and melts at 160—162°C.

In analogous manner, there are obtained:

- 55 N - [4 - (β - diethyl - cyanacetamido - ethyl) - benzenesulfonyl] - N' - cyclohexyl-urea, melting point 192—194°C. (from methanol) and
- N - [4 - (β - diethyl - cyanacetamido - ethyl) - benzenesulfonyl] - N' - butyl-urea, melting point 137—139°C. (from methanol).
- Furthermore, there are obtained:
- 60 from 4 - (β - α - bromo - isovaleramido) - ethyl) - benzenesulfonamide (melting point 156—158°C.):
- N - [4 - (β - α - bromo - isovaleramido) - ethyl) - benzenesulfonyl] - N' - cyclohexyl-urea, melting point 205—206°C. (from methanol/dimethylformamide);

N - [4 - (β - $\langle\alpha$ - bromo - isovaleramido $\rangle$ - ethyl) - benzenesulfonyl] - N'-butyl-urea, melting point 180—182°C. (from methanol); and

N - [4 - (β - $\langle\alpha$ - bromo - isovaleramido $\rangle$ - ethyl) - benzenesulfonyl] - N'-(4-methyl-cyclohexyl)-urea (trans), melting point 205—207°C. (from dimethylformamide/water).

EXAMPLE 19.

In a manner analogous to that of Example 6, paragraph 1, there is obtained:

N - [4 - (β - endomethylene - 2',5' - Δ^1 - tetrahydrobenzamidoethyl) - benzene-sulfonyl] - N'-(4-ethyl-cyclohexyl)-urea, melting point 178—180°C.;

N - [4 - (β - endomethylene - 2',5' - Δ^1 - tetrahydrobenzamidoethyl) - benzene-sulfonyl] - N'-(butyl)-urea, melting point 173—175°C.;

N - [4 - (β - endomethylene - 2',5' - Δ^1 - tetrahydrobenzamidoethyl) - benzene-sulfonyl] - N'-(4-methyl-cyclohexyl)-urea, melting point 191—193°C.

In a manner analogous to that of Example 6, paragraph 2, there is obtained:

N - [4 - (endomethylene - 2',5' - Δ^1 - tetrahydro - benzamidomethyl) - benzenesulfonyl] - N'-(4-ethylcyclohexyl)-urea, melting point 194—196°C.

In a manner analogous to that of Example 6, paragraph 3, there are obtained:

N - [4 - (β - endomethylene - 2',5' - hexahydrobenzamido - ethyl) - benzene-sulfonyl] - N'-(4-ethyl-cyclohexyl)-urea, melting point 196—198°C.; and

N - [4 - (β - endomethylene - 2',5' - hexahydrobenzamido - ethyl) - benzene-sulfonyl] - N'-butyl-urea, melting point 193—195°C.

In a manner analogous to that of Example 6, there are obtained: from 4 - (endomethylene - 2',5' - hexahydrobenzamido - methyl) - benzenesulfonamide (melting point 166—168°C.):

N - [4 - (endomethylene - 2',5' - hexahydrobenzamido - methyl) - benzene-sulfonyl] - N'-(4-methyl-cyclohexyl)-urea, melting point 180—182°C.; and

N - [4 - (endomethylene - 2',5' - hexahydrobenzamido - methyl) - benzene-sulfonyl] - N'-butyl-urea, melting point 169—171°C.

EXAMPLE 20.

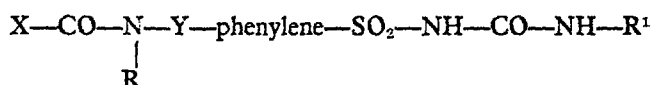
In a manner analogous to that of Example 3, there are obtained: from 4 - (β,β' - isopropoxy - propionamido - ethyl) - benzenesulfonamide (melting point 128—131°C.):

N - [4 - (β,β' - isopropoxy - propionamido - ethyl) - benzenesulfonyl] - N'-cyclohexyl-urea, melting point 148—150°C.; and

N - [4 - (β,β' - isopropoxy - propionamido - ethyl) - benzenesulfonyl] - N'-(4-ethyl-cyclohexyl)-urea, melting point 169—171°C.

WHAT WE CLAIM IS:—

1. Compounds of the general formula



in which

R is a hydrogen atom or a lower alkyl or a phenyl lower alkyl radical,

R¹ is

(a) an alkyl, alkenyl or mercaptoalkyl radical of 2 to 8 carbon atoms each,

(b) an alkoxyalkyl, alkylmercaptoalkyl or alkylsulphinylalkyl radical of 4 to 8 carbon atoms each, at least two of which carbon atoms form the alkylene portion of the alkoxyalkyl, alkylmercaptoalkyl or alkylsulphinylalkyl radical,

(c) a phenyl lower alkyl or a phenyl cyclopropyl radical,

(d) A cyclohexyl lower alkyl, cycloheptylmethyl, cycloheptylethyl or cyclooctyl-methyl radical,

(e) An endoalkylene-cyclohexyl, endoalkylene cyclohexenyl, endoalkylene-cyclohexyl methyl or endoalkylene cyclohexenylmethyl radical of 1 or 2 endo-alkylene carbon atoms each,

(f) a lower alkyl-cyclohexyl or lower alkoxy cyclohexyl radical,

(g) a cycloalkyl radical of 5 to 8 carbon atoms,

(h) a cyclohexenyl or cyclohexenylmethyl radical,

N - [4 - (β - α - bromo - isovaleramido) - ethyl) - benzenesulfonyl] - N'-butyl-urea, melting point 180—182°C. (from methanol); and

N - [4 - (β - α - bromo - isovaleramido) - ethyl) - benzenesulfonyl] - N'-(4-methyl-cyclohexyl)-urea (trans), melting point 205—207°C. (from dimethylformamide/water).

EXAMPLE 19.

In a manner analogous to that of Example 6, paragraph 1, there is obtained:

N - [4 - (β - endomethylene - 2',5' - Δ^3 - tetrahydrobenzamidoethyl) - benzenesulfonyl] - N'-(4-ethyl-cyclohexyl)-urea, melting point 178—180°C.;

N - [4 - (β - endomethylene - 2',5' - Δ^3 - tetrahydrobenzamidoethyl) - benzenesulfonyl] - N'-(butyl)-urea, melting point 173—175°C.;

N - [4 - (β - endomethylene - 2',5' - Δ^3 - tetrahydrobenzamidoethyl) - benzenesulfonyl] - N'-(4-methyl-cyclohexyl)-urea, melting point 191—193°C.

In a manner analogous to that of Example 6, paragraph 2, there is obtained:

N - [4 - (endomethylene - 2',5' - Δ^3 - tetrahydro - benzamidomethyl) - benzenesulfonyl] - N'-(4-ethylcyclohexyl)-urea, melting point 194—196°C.

In a manner analogous to that of Example 6, paragraph 3, there are obtained:

N - [4 - (β - endomethylene - 2',5' - hexahydrobenzamido - ethyl) - benzenesulfonyl] - N'-(4-ethyl-cyclohexyl)-urea, melting point 196—198°C.; and

N - [4 - (β - endomethylene - 2',5' - hexahydrobenzamido - ethyl) - benzenesulfonyl] - N'-butyl-urea, melting point 193—195°C.

In a manner analogous to that of Example 6, there are obtained:

from 4 - (endomethylene - 2',5' - hexahydrobenzamido - methyl) - benzenesulfonamide (melting point 166—168°C.):

N - [4 - (endomethylene - 2',5' - hexahydrobenzamido - methyl) - benzenesulfonyl] - N'-(4-methyl-cyclohexyl)-urea, melting point 180—182°C.; and

N - [4 - (endomethylene - 2',5' - hexahydrobenzamido - methyl) - benzenesulfonyl] - N'-butyl-urea, melting point 169—171°C.

EXAMPLE 20.

In a manner analogous to that of Example 3, there are obtained:

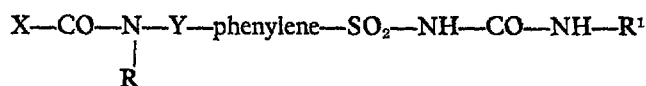
from 4 - (β,β' - isopropoxy - propionamido - ethyl) - benzenesulfonamide (melting point 128—131°C.):

N - [4 - (β,β' - isopropoxy - propionamido - ethyl) - benzenesulfonyl] - N'-cyclohexyl-urea, melting point 148—150°C.; and

N - [4 - (β,β' - isopropoxy - propionamido - ethyl) - benzenesulfonyl] - N'-(4-ethyl-cyclohexyl)-urea, melting point 169—171°C.

WHAT WE CLAIM IS:—

1. Compounds of the general formula



in which

R is a hydrogen atom or a lower alkyl or a phenyl lower alkyl radical,

R¹ is

(a) an alkyl, alkenyl or mercaptoalkyl radical of 2 to 8 carbon atoms each,

(b) an alkoxyalkyl, alkylmercaptoalkyl or alkylsulphinylalkyl radical of 4 to 8 carbon atoms each, at least two of which carbon atoms form the alkylene portion of the alkoxyalkyl, alkylmercaptoalkyl or alkylsulphinylalkyl radical,

(c) a phenyl lower alkyl or a phenyl cyclopropyl radical,

(d) A cyclohexyl lower alkyl, cycloheptylmethyl, cycloheptylethyl or cyclooctylmethyl radical,

(e) An endoalkylene-cyclohexyl, endoalkylene cyclohexenyl, endoalkylene-cyclohexyl methyl or endoalkylene cyclohexenylmethyl radical of 1 or 2 endoalkylene carbon atoms each,

(f) a lower alkyl-cyclohexyl or lower alkoxy cyclohexyl radical,

(g) a cycloalkyl radical of 5 to 8 carbon atoms,

(h) a cyclohexenyl or cyclohexenylmethyl radical,





- (i) a heterocyclic nucleus containing, in addition to 4 or 5 carbon atoms, one oxygen or sulphur atom and up to two ethylenic double linkages, or
- (j) a heterocyclic nucleus as defined under (i) bound to the adjacent nitrogen atom via a methylene group,
- 5 X is 5
- (a) an alkyl, alkenyl, alkoxy alkyl or alkylmercaptoalkyl radical of 4 to 11 carbon atoms,
- (b) a cycloalkyl, cycloalkenyl, cycloalkyl-lower alkyl, cycloalkenyl-lower alkyl, lower alkyl-cycloalkyl or lower alkyl-cycloalkenyl radical of 4 to 8 ring carbon atoms, 10
- (c) An endoalkylene-cyclohexyl or endoalkylene-cyclohexenyl radical of 1 or 2 endoalkylene carbon atoms,
- (d) a cycloalkoxy-alkyl, cycloalkylmercapto-alkyl, cycloalkyl-alkoxy-alkyl, cycloalkyl-alkylmercapto-alkyl radical of 4 to 11 carbon atoms, or
- 15 (e) an alkyl, cycloalkyl or cycloalkylalkyl radical substituted by one or two substituents selected from chlorine and bromine atoms and cyano groups. 15
- Y is a hydrocarbon radical of 1 to 4 carbon atoms.
2. Compounds as claimed in claim 1, wherein R is a hydrogen atom.
3. Compounds as claimed in claim 1, wherein R¹ is a cyclohexyl radical.
- 20 4. Compounds as claimed in claim 1, wherein R¹ is a lower alkyl-cyclohexyl radical. 20
5. Compounds as claimed in claim 1, wherein X is a cycloalkyl radical of 4 to 8 carbon atoms.
6. Compounds as claimed in claim 1, wherein X is an alkyl radical of 4 to 11 carbon atoms. 25
7. Compounds as claimed in claim 1, wherein Y is a dimethylene group.
8. N-[4-(β -capronamido-ethyl)-benzenesulphonyl]-N'-(4-methyl-cyclohexyl)-urea.
9. N - [4 - (β - trimethylacetamido - ethyl) - benzenesulphonyl] - N' - (4-methyl-cyclohexyl)-urea.
- 30 10. N - [4 - (β - trimethylacetamido - ethyl) - benzenesulphonyl] - N' - cyclohexyl-urea. 30
11. N - [4 - (β - Δ^3 - cyclohexenecarbonamido - ethyl) - benzenesulphonyl] - N' - methyl-cyclohexyl-urea.
12. N - [4 - (β - cyclohexane carbonamido - ethyl) - benzenesulphonyl] - N' - (4-methyl-cyclohexyl)-urea. 35
13. A physiologically tolerable salt of a compound as claimed in claim 1 with a base.
14. A physiologically tolerable salt of a compound as claimed in any one of claims 2 to 12 with a base.
- 40 15. A compound as claimed in claim 1 and described in any one of the Examples herein. 40
16. A process for the manufacture of a compound as claimed in any one of claims 1 to 12, conducted substantially as hereinbefore described.
- 45 17. A pharmaceutical preparation for lowering the blood sugar level in the treatment of diabetes mellitus, which comprises a benzenesulphonyl-urea as claimed in any one of claims 1 to 12 in admixture or conjunction with a pharmaceutically suitable carrier. 45
18. A pharmaceutical preparation for lowering the blood sugar level in the treatment of diabetes mellitus, which comprises a salt as claimed in claim 13 or 14 in admixture or conjunction with a pharmaceutically suitable carrier. 50
19. A pharmaceutical preparation as claimed in claim 17 or claim 18, which is in the form of an oral preparation.
20. A pharmaceutical preparation as claimed in any one of claims 17 to 19, which is in unit dosage form and contains from 0.5 to 100 milligrams of the benzenesulphonyl-urea or a salt thereof. 55
21. A pharmaceutical preparation as claimed in claim 20, which contains from 2 to 10 milligrams of the benzenesulphonyl-urea or a salt thereof.

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