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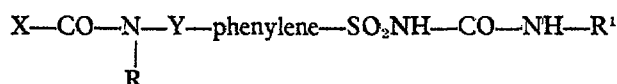
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COMPLETE SPECIFICATION

Benzenesulphonyl-Ureas and process for preparing them

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

The present invention provides benzenesulphonyl-ureas of the general formula



which as such or in the form of their physiologically tolerable salts show hypoglycemic properties and are distinguished by a strong and — above all — a long-lasting blood sugar lowering action.

In the formula

R represents hydrogen, lower alkyl or phenyl-lower alkyl,

R¹ represents:

- a) alkyl, alkenyl or mercaptoalkyl having 2 to 8 carbon atoms,
- b) alkoxyalkyl, alkylmercaptoalkyl or alkylsulphinylalkyl having 4 to 8 carbon of which at least 2 belong to the alkylene part of the alkoxy-alkyl, alkylmercaptoalkyl or alkylsulphinylalkyl,
- c) phenyl-lower alkyl, phenylcyclopropyl,
- d) cyclohexyl-lower alkyl, cycloheptylmethyl, cycloheptylethyl or cyclooctylmethyl,
- e) endoalkylene-cyclohexyl, endoalkylene-cyclohexenyl, endoalkylene-cyclohexylmethyl or endoalkylene-cyclohexenylmethyl each containing 1 or 2 endoalkylene carbon atoms,
- f) lower alkylcyclohexyl or lower alkoxy-cyclohexyl,
- g) cycloalkyl having 5 to 8 carbon atoms,
- h) cyclohexenyl or cyclohexenylmethyl,
- i) a heterocyclic ring with 4 or 5 carbon atoms and 1 oxygen atom or 1 sulphur atom and which may also contain up to 2 ethylenic double linkages, or
- k) a heterocyclic ring linked to the nitrogen atom by means of a methylene group and containing 4 or 5 carbon atoms and 1 oxygen atom or 1 sulphur atom and which may also contain up to 2 ethylenic double linkages,

X represents:

- a) thiophenyl or thiophenoxy which may contain 1 or 2 substituents selected from halogen atoms, lower alkyl, lower alkoxy, lower alkenyloxy, lower alkoxy-lower alkoxy, lower phenalkoxy and aryl groups, and a polymethylene chain of 3 or 4 carbon atoms linked by both ends to the thiophenyl nucleus,
- b) furyl which may contain 1 or 2 substituents selected from halogen atoms and methyl groups,

c) pyridyl which may carry 1 or 2 substituents selected from halogen atoms and lower alkyl groups, the heterocyclic ring system mentioned under (a), (b) or (c) being linked either directly or by means of a hydrocarbon chain having 1 or 2 carbon atoms to the adjacent carbonyl group, and

Y represents a hydrocarbon chain having 1 to 4 carbon atoms.

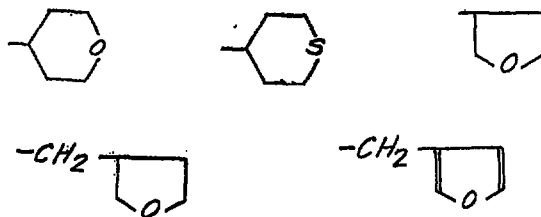
In the above and the following definitions "lower alkyl" always means alkyl having 1 to 4 carbon atoms in a straight or branched chain. "Lower acyl" stands for an acyl radical (organic acid radical) having up to 4 carbon atoms, preferably a straight-chain or branched alkanoyl radical of corresponding chain length.

In accordance with the definitions given above, R may represent, for instance, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, benzyl, α - or β -phenylethyl, α -, β - or γ -phenylpropyl. Compounds in which R stands for methyl or benzyl and, above all, those in which R represents hydrogen, are preferred.

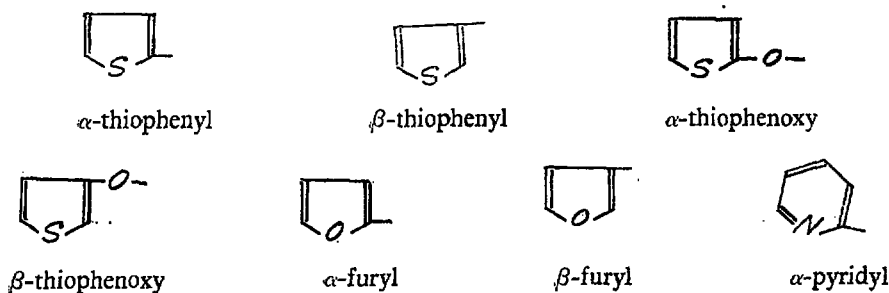
R¹ may represent, for instance, ethyl, propyl, isopropyl butyl, isobutyl, secondary butyl, straight-chain or branched amyl (pentyl), hexyl, heptyl or octyl; the radicals with an ethylenic double linkage, such as allyl or crotyl, corresponding to the above-mentioned hydrocarbon radicals, further alkyls with 2 to 8 carbon atoms carrying, in addition, a mercapto group, for instance β -mercaptoethyl or higher mercaptoalkyls. R¹ may likewise represent, for example γ -methoxypropyl, δ -methoxy-n-butyl, β -ethoxyethyl, γ -ethoxypropyl, δ -ethoxy-butyl or higher alkyloxyethyls, -propyls or -butyls as well as the corresponding groups in which the oxygen atom is replaced by a sulphur atom or by the member —SO—. Furthermore, R¹ may stand for benzyl, α -phenylethyl, β -phenylethyl, α -, β - or γ -phenylpropyl or phenylbutyls.

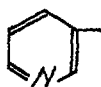
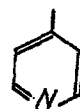
Within the scope of the invention there are particularly preferred compounds containing as R¹ a cycloaliphatic hydrocarbon group which may be substituted by alkyl or alkoxy or linked to the nitrogen atom by means of alkylene. Said radicals comprise, for example, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, methylcyclohexyl, ethylcyclohexyl, propylcyclohexyl and isopropyl-cyclohexyl, methoxycyclohexyl, ethoxy-cyclohexyl, propoxy-cyclohexyl and isopropoxycyclohexyl. The alkyl or alkoxy groups may be present in the 2-, 3- or — preferably — in the 4-position, in the cis- as well as in the trans-position. Furthermore, there may be mentioned: cyclohexylmethyl, α - or β -cyclohexylethyl, cyclohexylpropyls, endomethylene-cyclohexyl (2:2:1-tricycloheptyl), endoethylene-cyclohexyl (2:2:2-tricyclooctyl), endomethylene-cyclohexenyl, endoethylene-cyclohexenyl, endomethylene-cyclohexylmethyl, endoethylene-cyclohexylmethyl, endomethylene-cyclohexenylmethyl or endoethylene-cyclohexenylmethyl, α - or β -phenylcyclopropyl in the cis as well as in the trans form.

Finally, there are suitable as R¹ heterocyclic rings containing in addition to 4 or 5 carbon atoms 1 oxygen or sulphur atom and, if desired, up to 2 double linkages and which may be bound by means of a methylene group to the adjacent nitrogen atom. Examples of said heterocyclic rings are:



As the member X of the above formula there may be mentioned the following heterocyclic ring systems:



 β -pyridyl γ -pyridyl

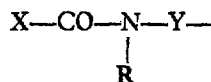
These ring systems which may contain, in addition, in any position desired one or two substituents of the type mentioned on page 2 (which, in the case of two substituents, may be the same or different), are each linked to the adjacent carbonyl group by means of the free valence given in the above formulae, either directly or by means of a hydrocarbon bridge with 1 or 2 carbon atoms. Said bridges are, for example, $-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{CH}_2-\text{CH}_2-$ or $-\text{CH}=\text{CH}-$.

Examples of the bridge member Y are: $-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-\text{CH}_2-$, $-\text{CH}_2-\text{CH}(\text{CH}_3)-$, $-\text{C}(\text{CH}_3)_2-$, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-\text{CH}_2-\text{CH}_2-$, $-\text{CH}_2-\text{CH}(\text{CH}_3)-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-\text{CH}(\text{CH}_3)-$, $-\text{CH}(\text{CH}_3)-\text{CH}_2-\text{CH}_2-$, $-\text{CH}_2-\text{CH}(\text{CH}_3)-\text{CH}_2-$, $-\text{CH}_2-\text{C}(\text{CH}_3)_2-$, $-\text{CH}(\text{C}_2\text{H}_5)-$, $-\text{C}(\text{CH}_3)(\text{C}_2\text{H}_5)-$.

The phenylene radical designated in the formula by "phenylene" is preferably unsubstituted. It may, however, also be mono- or poly-substituted by halogen, lower alkyl, or lower alkoxy. It may contain the remaining parts of the molecule in ortho-, meta- or para-position to one another, the para-position being preferred.

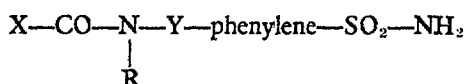
The present invention also provides a process for the manufacture of the new compounds which comprises

- a) reacting a benzenesulphonyl-isocyanate, benzenesulphonyl-carbamic acid ester, benzenesulphonyl-thiocarbamic acid ester, benzenesulphonyl-carbamic acid halide or a benzenesulphonyl-urea carrying the substituent



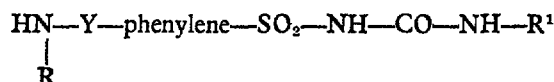
with an R^1 -substituted amine or, if desired, a salt thereof;

- b) reacting a benzenesulphonamide of the formula



or, if desired, a salt thereof with an R^1 -substituted isocyanate, carbamic acid ester, thiocarbamic acid ester, carbamic acid halide or a urea;

- c) reacting a correspondingly substituted benzenesulphonyl halide with an R^1 -substituted urea;
- d) hydrolysing a correspondingly substituted benzenesulphonyl-isourea-ether, benzenesulphonyl-isothiourethane or benzenesulphonyl-parabanic acid;
- e) replacing the sulphur atom in correspondingly substituted benzenesulphonyl-thiourea by an oxygen atom by a known method (by which is to be understood herein a method known to be in actual use or described in the relevant literature);
- f) oxidizing a corresponding benzenesulphonyl-urea or benzenesulphenyl-urea, or
- g) introducing a radical $\text{X}-\text{CO}-$ by acylation into a benzenesulphonyl-urea of the formula



and treating the reaction product with an alkaline agent if salt formation is desired.

According to the nature of the member X, the one or the other of the processes mentioned above may in single cases be unsuitable for the preparation of the individual compounds covered by the general formula or may at least require measures for the protection of active groups. Said cases which are comparatively unusual are easily

recognized by the expert and it does not cause any difficulties to apply with success another method of synthesis of those described above.

Instead of the benzenesulphonyl-isocyanates there may also be used the products obtained by reaction of benzenesulphonyl-isocyanates with acid amides, such, for example, as caprolactam or butyrolactam, moreover those obtained by reaction with weakly basic amines, for instance carbazoles.

The above-mentioned benzenesulphonyl-carbamic acid esters of benzenesulphonyl-thiocarbamic acid esters may contain in the alcohol component a low-molecular alkyl radical or a phenyl radical. The same applies to the R¹-substituted carbamic acid esters or the corresponding mono-thiocarbamic acid esters. As a low-molecular or lower alkyl radical in the sense of the invention is to be understood, in each case, an alkyl radical having at most 4 carbon atoms.

Suitable carbamic acid halides are, in the first place, the chlorides.

The benzenesulphonyl-ureas to be used as starting substances for the process may be unsubstituted at the side of the urea molecule which is opposite to the sulphonyl group or may, preferably, be mono- or di-substituted by lower alkyl radicals or aryl radicals. Instead of benzenesulphonyl-ureas substituted in said manner there can likewise be used corresponding N-benzenesulphonyl-N'-acyl-ureas (acyl = lower aliphatic acyl such, for example, as acetyl, propionyl or butyryl, but also benzoyl) and likewise bis-(benzenesulphonyl)-ureas. It is, for instance, possible to treat said bis-(benzenesulphonyl)-ureas or N-benzenesulphonyl-N'-acyl-ureas with amines R¹NH₂ and to heat the salts obtained to elevated temperatures, particularly above 100°C.

It is likewise possible to start from a urea of the formula R¹-NH-CO-NH₂ or from an acylated urea of the formula R¹-NH-CO-NH-acyl, wherein acyl represents an aliphatic or aromatic acid radical preferably of low molecular weight or the nitro group, or from a phenyl urea of the formula R¹-NH-CO-NH-C₆H₅, or from a diphenyl-urea of the formula R¹-NH-CO-N(C₆H₅)₂, in which case the phenyl radicals may be substituted and may be linked with one another directly or by means of a bridge member such, for example, as -CH₂-, -NH-, -O- or -S-, or from N:N'-disubstituted ureas of the formula R¹-NH-CO-NH-R¹ and to react it with a benzenesulphonamide which is substituted by X-CON-Y-

R

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

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

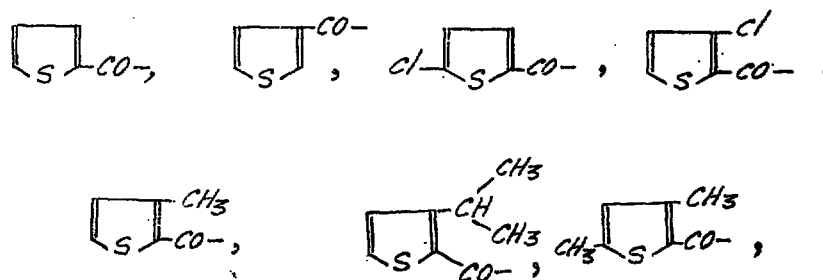
As regards the reaction conditions, the forms of carrying out the process of the invention may, in general, vary within wide limits and can be adapted to each individual case.

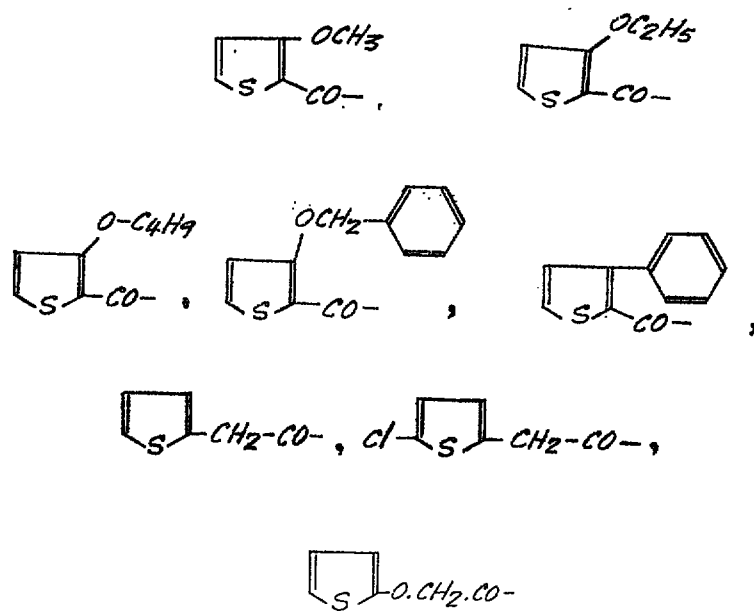
For example, the reactions can be carried out with the use of solvents either at room temperature or at an elevated temperature.

As starting substances there may be used, on the one hand, compounds containing a benzene radical which is substituted by the group X-CON-Y-. As examples of the

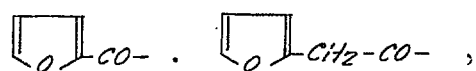
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component X-CO- of said formula there may be mentioned the following:—

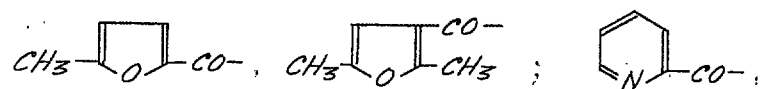
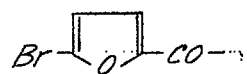
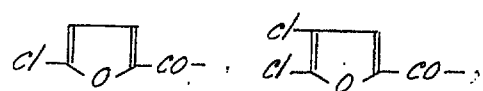




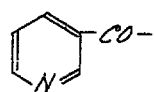
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hydroxides, alkali metal carbonates or alkaline earth metal carbonates, alkali metal bicarbonates or alkaline earth metal bicarbonates.

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

As pharmaceutical preparations there enter into consideration preferably tablets, and as carriers there may be used the usual pharmaceutical adjuvants and carriers such, for example, as talc, starch, lactose, tragacanth or magnesium stearate.

A preparation containing one of the above-described benzenesulphonyl-ureas as active substance, for instance, a tablet or a powder with or without the above-mentioned additions, is favourably brought into a suitable dosage unit form. The dose chosen should comply with the activity of the benzenesulphonyl-urea used and the desired effect. The dosage per unit amounts advantageously to about 0.5 to 100 milligrams, preferably to 2—10 milligrams, but considerably higher or lower dosage units can likewise be used which, if desired, are divided or multiplied prior to application.

The following Examples illustrate the invention:—

EXAMPLE 1

N-[4-(β -thiophene-2-carbonamido-ethyl)-benzenesulphonyl]-N'-cyclohexyl urea

15.5 Grams of 4-(β -thiophene-2-carbonamido-ethyl)-benzenesulphonamide (melting point 238°C; prepared from 4-(β -aminoethyl)-benzenesulphonamide and thiophene-2-carboxylic acid chloride) are dissolved in 200 ml of acetone by adding 2 grams of NaOH and water. 6.5 Grams of cyclohexyl isocyanate are dropped into the solution while stirring at room temperature, stirring is continued for 2 hours, the slightly turbid solution is filtered and the filtrate acidified with hydrochloric acid. The precipitated reaction product is reprecipitated from ammonia of 1% strength and recrystallized from ethanol/water. The N-[4-(β -thiophene-2-carbonamido-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea obtained melts at 194—196°C.

In an analogous manner there are obtained:

N - [4 - (β - thiophene - 2 - carbonamido - ethyl) - benzenesulphonyl] - N'-butyl-urea (melting point: 213—215°C);

N - [4 - (β - thiophene - 2 - carbonamido - ethyl) - benzenesulphonyl] - N'-(4-ethyl-cyclohexyl)-urea (melting point: 192—194°C);

N - [4 - (β - thiophene - 2 - carbonamido - ethyl) - benzenesulphonyl] - N'-(4-methyl-cyclohexyl)-urea (melting point: 181—183°C).

In an analogous manner there are obtained from 4-(thiophene-2-carbonamido-methyl)-benzenesulphonamide (melting point: 219—221°C):

N - [4 - (thiophene - 2 - carbonamido - methyl) - benzenesulphonyl] - N' - butyl-urea (melting point: 155—157°C);

N - [4 - (thiophene - 2 - carbonamido - methyl) - benzenesulphonyl] - N' - cyclohexyl-urea (melting point: 187—188°C);

N - [4 - (thiophene - 2 - carbonamido - methyl) - benzenesulphonyl] - N' - (4 - ethyl-cyclohexyl)-urea (melting point: 196—198°C).

EXAMPLE 2

N-[4-(β -5-chloro-thiophene-2-carbonamidoethyl)-benzenesulphonyl]-N'-cyclohexyl-urea

17.2 Grams of 4-(β -5-chloro-thiophene-2-carbonamidoethyl)-benzenesulphonamide (melting point 280°C; prepared from 4-(β -aminoethyl)-benzenesulphonamide and 5 - chloro - thiophene - 2 - carboxylic acid chloride) are suspended in 200 ml of acetone and dissolved by the addition of 2 grams of sodium hydroxide and water. 6.5 Grams of cyclohexyl isocyanate are dropped into this solution and the whole is stirred for 2 hours. The slightly turbid solution is filtered with suction, the filtrate combined with water and hydrochloric acid, and the precipitated product recrystallized from ethanol/water. The N-[4-(β -5-chloro-thiophene-2-carbonamido-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea obtained melts at 189—191°C.

In an analogous manner there are obtained:

N - [4 - (β - 5 - chloro - thiophene - 2 - carbonamidoethyl) - benzenesulphonyl] - N'-butyl-urea (melting point: 188—190°C);

N - [4 - (β - 5 - chloro - thiophene - 2 - carbonamidoethyl) - benzenesulphonyl] - N'-(4-methyl-cyclohexyl)-urea (melting point: 190—192°C);

N - [4 - (β - 5 - chloro - thiophene - 2 - carbonamidoethyl) - benzenesulphonyl] - N'-(4-ethyl-cyclohexyl)-urea (melting point: 191—193°C).

EXAMPLE 3

- 5 N-[4-(β -3-methoxythiophene-2-carbonamidoethyl)-benzenesulphonyl]-
N'-cyclohexyl-urea 5
- 10 10 Grams of 4 - (β - 3 - methoxythiophene - 2 - carbonamidoethyl) - benzene-
sulphonamide (melting point: 201—203°C; from dimethylformamide/water) are dis-
solved in 15 ml of 2N-sodium hydroxide solution and 30 ml of acetone, and 3.9
grams of cyclohexyl isocyanate are added dropwise at 0—5°C. The reaction mixture
is stirred for 3 hours, diluted with water and filtered, and the filtrate is acidified by
means of dilute hydrochloric acid. The N-[4-(β -3-methoxythiophene-2-carbonamido-
ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea which precipitates in the form of crystals
is recrystallized from dimethylformamide/water and melts at 193—194°C.
- 15 In an analogous manner there are obtained:
N - [4 - (β - 3 - methoxythiophene - 2 - carbonamidoethyl) - benzenesulphonyl] - N'-
butyl-urea (melting point: 173—175°C) (from methanol), and
N - [4 - (β - 3 - methoxythiophene - 2 - carbonamidoethyl) - benzenesulphonyl] - N'-
(4-methylcyclohexyl)-urea (melting point: 190—192°C) (from dimethylform-
amide/water).
- 20 In an analogous manner there are obtained from 4-(β -3-ethoxythiophene-2-
carbonamido-ethyl)-benzenesulphonamide (melting point: 177°C):
N - [4 - (β - 3 - ethoxythiophene - 2 - carbonamido - ethyl) - benzenesulphonyl] - N'-
cyclooctyl-urea (melting point: 158—160°C) (from dimethylformamide/
methanol);
25 N - [4 - (β - 3 - ethoxythiophene - 2 - carbonamido - ethyl) - benzenesulphonyl] - N'-
cyclohexyl-urea (melting point: 174—175°C) (from methanol/dimethylform-
amide);
N - [4 - (β - 3 - ethoxythiophene - 2 - carbonamido - ethyl) - benzenesulphonyl] - N'-
butyl-urea (melting point: 146—147°C) (from dimethylformamide/water), and
30 N - [4 - (β - 3 - ethoxythiophene - 2 - carbonamido - ethyl) - benzenesulphonyl] - N'-
(4-methylcyclohexyl)-urea (melting point: 174—176°C) (from dimethylform-
amide/water).
- In an analogous manner there are obtained from 4- β -3,5-dimethylthiophene-2-
carbonamido-ethyl)-benzenesulphonamide (melting point: 176—177°C):
35 N - [4 - (β - 3,5 - dimethylthiophene - 2 - carbonamido - ethyl) - benzenesulphonyl] -
N'-cyclohexyl-urea (melting point 189—190°C (from dimethylformamide/water),
and N - [4 - (β - 3,5 - dimethylthiophene - 2 - carbonamido - ethyl) - benzene-
sulphonyl]-N'-(4-methylcyclohexyl)-urea (melting point: 173—175°C) (from
dimethylformamide/water).
- 40 In an analogous manner there are obtained from 4-(β -3-methylthiophene-2-
carbonamido-ethyl)-benzenesulphonamide (melting point: 198—200°C):
N - [4 - (β - 3 - methylthiophene - 2 - carbonamido - ethyl) - benzenesulphonyl] -
N'-cyclooctyl-urea (melting point: 203—205°C) (from dimethylformamide/
water);
45 N - [4 - (β - 3 - methylthiophene - 2 - carbonamido - ethyl) - benzenesulphonyl] -
N'-cyclohexyl-urea (melting point: 183—184°C) (from dimethylformamide/
water);
N - [4 - (β - 3 - methylthiophene - 2 - carbonamido - ethyl) - benzenesulphonyl] -
N'-butyl-urea (melting point: 175—177°C) (from dimethylformamide/water),
50 and
N - [4 - (β - 3 - methylthiophene - 2 - carbonamido - ethyl) - benzenesulphonyl] -
N'-(4-methylcyclohexyl)-urea (trans-form) (melting point: 201—203°C) (from
dimethylformamide/water).
- In an analogous manner there are obtained from 4-(β -3-chlorothiophene-2-carbon-
amido-ethyl)-benzenesulphonamide (melting point: 211—213°C):
55 N - [4 - (β - 3 - chlorothiophene - 2 - carbonamido - ethyl) - benzenesulphonyl] -
N'-cyclohexyl-urea (melting point: 183—184°C) (from dimethylformamide/
water),
N - [4 - (β - 3 - chlorothiophene - 2 - carbonamido - ethyl) - benzenesulphonyl] -
N'-butyl-urea (melting point: 189—190°C) (from methanol),
60 N - [4 - (β - 3 - chlorothiophene - 2 - carbonamido - ethyl) - benzenesulphonyl] -
N'-(4-methyl-cyclohexyl)-urea (trans-form) (melting point: 207—209°C) (from
dimethylformamide/water), and

N - [4 - (β - 3 - chlorothiophene - 2 - carbonamido - ethyl) - benzenesulphonyl] - N'-(4-ethylcyclohexyl)-urea (transform) (melting point: 177—178°C) (from methanol).

EXAMPLE 4

5 N-[4-(β-3-benzyloxythiophene-2-carbonamido-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea 5

A mixture of 11.5 grams of N-[4-(β-3-benzyloxythiophene-2-carbonamidoethyl)-benzenesulphonyl]-urea (melting point: 109—110°C; from dimethylformamide/water), 300 ml of toluene, 30 ml of glycolmonomethyl ether, 1.65 grams of glacial acetic acid and 2.8 grams of cyclohexylamine is heated under reflux for 5 hours, while stirring. The mixture is concentrated *in vacuo* and the residue triturated with methanol. The N - [4 - (β - 3 - benzyloxythiophene - 2 - carbonamido - ethyl) - benzenesulphonyl] - N'-cyclohexyl-urea which is obtained in the form of crystals is filtered with suction and recrystallized from methanol/dimethylformamide. Melting point: 167—168°C.

EXAMPLE 5

15 N-[4-(β-3-benzyloxythiophene-2-carbonamido-ethyl)-benzenesulphonyl]-N'-(4-methylcyclohexyl)-urea 15

23.8 Grams of N-[4-(β-3-benzyloxythiophene-2-carbonamido-ethyl)-benzenesulphonyl]-methyl-urethane (melting point: 163—164°C; from alcohol) are suspended in 50 ml of xylene and 5.8 grams of 4-methylcyclohexylamine are added dropwise at 70°C, while stirring. The temperature is raised to 120—130°C while the reaction sets in with the formation of methanol. The temperature is maintained at 130°C for 30 minutes, then the whole is allowed to cool, and the precipitated crude product is filtered with suction and recrystallized from methanol. The N-[4-(β-3-benzyloxythiophene-2-carbonamido-ethyl)-benzenesulphonyl]-N'-(4-methylcyclohexyl)-urea obtained melts at 153—155°C.

EXAMPLE 6

30 N-[4-(β-thiophene-2-carbonamido-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea 30

1.35 Grams of N-[4-(β-thiophene-2-carbonamido-ethyl)-benzenesulphonyl]-N'-cyclohexyl-thiourea (melting point: 181—183°C; prepared from 4-(β-thiophene-2-carbonamido-ethyl)-benzenesulphonamide and cyclohexyl-mustard oil) are dissolved in 3 ml of normal sodium hydroxide solution and 30 ml of water and the whole is added to a suspension of mercury oxide obtained by the dissolution of 0.81 grams of mercury (2) chloride in 15 ml of water and the addition of 3 ml of 2N-sodium hydroxide solution. The whole is heated to 40°C, stirred for 5 minutes at this temperature, the mercury sulphide precipitated is filtered, the filtrate acidified with dilute hydrochloric acid and the precipitated reaction product filtered with suction. After recrystallization from methanol the N - [4 - (β - thiophene - 2 - carbonamido - ethyl) - benzenesulphonyl]-N'-cyclohexyl-urea melts at 191—193°C.

EXAMPLE 7

45 N-[4-(β-thiophene-2-carbonamidoethyl)-benzenesulphonyl]-N'-cyclohexyl-urea 45

1.2 Grams of N - [4 - (β - thiophene - 2 - carbonamidoethyl) - benzenesulphonyl]-N'-cyclohexyl-isourea methyl ether (in the form of an oil obtained by treating N - [4 - (β - thiophene - 2 - carbonamidoethyl) - benzenesulphonyl] - N'-cyclohexyl-thiourea with mercury oxide in methanol) are heated for about 10 minutes on a steam bath together with 15 ml of concentrated hydrochloric acid. The reaction mixture is allowed to cool, diluted with water, and the reaction product filtered with suction. The N - [4 - (β - thiophene - 2 - carbonamidoethyl) - benzene - sulphonyl]-N'-cyclohexyl-urea is recrystallized from methanol and melts at 191—193°C.

EXAMPLE 8

55 N-[4-(β-furoylaminoethyl)-benzenesulphonyl]-N'-cyclohexyl-urea 55

14.7 Grams of 4 - (β - furoylaminoethyl) - benzenesulphonamide (melting point: 228—230°C; prepared by the reaction of 4-(β-aminoethyl)-benzenesulphonamide with pyromucic acid chloride) are suspended in 200 ml of acetone and dissolved by the addition of 2 grams of sodium hydroxide and water. 6.5 Grams of cyclohexyl isocyanate are dropped into the solution while stirring at room temperature, and stirring is continued for 2 hours. The fine precipitate formed is filtered with suction and the filtrate combined with water and hydrochloric acid. The product is filtered with suction and recrystallized from a mixture of ethanol and water. The N-[4-(β-

furoylaminoethyl)-benzenesulphonyl]-N'-cyclohexyl-urea obtained melts at 176—178°C.

In an analogous manner there are obtained:

- N - [4 - (β - furoylaminoethyl) - benzenesulphonyl] - N' - (4 - ethylcyclohexyl)-urea, melting at 196—198°C;
- 5 N - [4 - (β - furoylaminoethyl) - benzenesulphonyl] - N' - butyl-urea, melting at 201—203°C;
- N - [4 - (β - furoylaminoethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl)-urea, melting at 184—186°C;
- 10 N - [4 - (β - furoylaminoethyl) - benzenesulphonyl] - N' - (4 - isopropyl - cyclohexyl)-urea, melting at 209—211°C.
- In an analogous manner there are obtained from 4-(β -furoylaminopropyl)-benzenesulphonamide (melting point: 192—194°C):
- 15 N - [4 - (β - furoylaminopropyl) - benzenesulphonyl] - N' - cyclohexyl - urea, melting at 196—198°C;
- N - [4 - (β - furoylaminopropyl) - benzenesulphonyl] - N' - (4 - ethyl - cyclohexyl)-urea, melting at 179—181°C.

EXAMPLE 9

N(4-furoylaminomethyl-benzenesulphonyl)-N'-cyclohexyl-urea

- 28 Grams of 4-furoylaminomethyl-benzenesulphonamide (melting point 218—219°C) are suspended in 250 ml of acetone and dissolved by addition of 4 grams of sodium hydroxide and water. 12.5 Grams of cyclohexyl isocyanate are dropped in while stirring at room temperature, and stirring is continued for 2 hours. The slightly turbid solution is filtered, the filtrate is acidified after addition of water and the reaction product recrystallized from ethanol. The N-(4-furoylamino-methyl-benzenesulphonyl)-N'-cyclohexyl-urea obtained melts at 173—175°C.
- 25 In an analogous manner there are obtained:
- N - (4 - furoylaminomethyl - benzenesulphonyl) - N' - butyl - urea (melting point: 171—173°C), and
- 30 N - (4 - furoylaminomethyl - benzenesulphonyl) - N' - (4 - isopropyl - cyclohexyl)-urea (melting point: 190—192°C).

EXAMPLE 10

N-[4-(β -furyl-2-propionamidoethyl)-benzenesulphonyl]-N'-cyclohexyl-urea

- 15 Grams of 4-(β -furyl-2-propionamidoethyl)-benzenesulphonamide (melting point: 195—197°C; prepared from 4-(β -aminoethyl)-benzenesulphonamide and the mixed anhydride of furyl-2-propionic acid and carbonic acid semi-ester) are combined in 200 ml of acetone with a solution of 1.1 grams of sodium hydroxide solution in water. Water is added while stirring until a solution is formed, 6 grams of cyclohexyl isocyanate are dropped in at room temperature and stirring is continued for 2 hours. The reaction mixture is filtered and water and hydrochloric acid are added. The reaction product is filtered with suction and recrystallized from a mixture of ethanol and water. The N-[4-(β -furyl-2-propionamidoethyl)-benzenesulphonyl]-N'-cyclohexyl-urea obtained melts at 170—172°C.
- 40 In an analogous manner are obtained:
- 45 N - [4 - (β - furyl - 2 - propionamidoethyl) - benzenesulphonyl] - N' - (4 - ethyl-cyclohexyl)-urea (melting point: 141—143°C), and
- N - [4 - (β - furyl - 2 - propionamidoethyl) - benzenesulphonyl] - N' - butyl - urea (melting point: 132—134°C).
- In an analogous manner there are obtained from
- 50 4 - (β - furfurylidene - acetamidoethyl) - benzenesulphonamide (melting point: 240°C; prepared from 4-(β -aminoethyl)-benzenesulphonamide and furylacrylic acid chloride):
- N - [4 - (β - furfurylidene - acetamidoethyl) - benzenesulphonyl] - N' - cyclohexyl-urea (melting point: 200°C), and
- 55 N - [4 - (β - furfurylidene - acetamidoethyl) - benzenesulphonyl] - N' - butyl - urea (melting point: 199°C).

EXAMPLE 11

N-[4-(5-chloro-furoylaminomethyl)-benzenesulphonyl]-N'-butyl-urea

- 11 Grams of 4-(5-chloro-furoylaminomethyl)-benzenesulphonamide are dissolved in 150 ml of acetone by the addition of 1.4 grams of sodium hydroxide solution and water. 3.5 Grams of butyl isocyanate are dropped in at room temperature and the whole is stirred for 2 hours. The slightly turbid solution is filtered with suction, the filtrate is combined with water and hydrochloric acid and the product filtered with

suction. The N - [4 - (5 - chloro - furoylaminomethyl) - benzenesulphonyl] - N'-butyl-urea obtained is recrystallized from ethanol/water and melts at 161—162°C.

EXAMPLE 12

N-[4-(β-furoylaminoethyl)-benzenesulphonyl]-N'-cyclohexyl-urea

17.6 Grams of N - [4 - (β - furoylaminoethyl) - benzenesulphonyl] - carbamic acid methyl ester (melting point: 182—184°C; prepared from 4-(β-furoylaminoethyl)-benzenesulphonamide and chloroformic acid methyl ester in the presence of potassium carbonate) are suspended in 50 ml of xylene and 5 grams of cyclohexylamine are dropwise added at about 60—80°C, while stirring. While the temperature is raised to 120—130°C the reaction sets in with the evolution of methanol, and the whole is stirred for about 1 hour at this temperature. After cooling, the precipitated reaction product is filtered with suction and recrystallized from a mixture of ethanol and water. The N - [4 - (β - furoylaminoethyl) - benzenesulphonyl] - N' - cyclohexyl-urea obtained melts at 176—178°C.

EXAMPLE 13

N-[4-(β-furoylaminoethyl)-benzenesulphonyl]-N'-cyclohexyl-urea

8 Grams of N-[4-(β-furoylaminoethyl)-benzenesulphonyl]-urea (melting point: 185—187°C; prepared from 4-(β-furoylaminoethyl)-benzenesulphonamide and potassium cyanate are heated under reflux for 5 hours, while stirring, in 250 ml of toluene containing 1.65 grams of glacial acetic acid and 2.9 grams of cyclohexylamine. After cooling the whole is concentrated *in vacuo*, the residue is treated with some alcohol and water and the reaction product filtered with suction. The N-[4-(β-furoylaminoethyl)-benzenesulphonyl]-N'-cyclohexyl-urea obtained is recrystallized from ethanol/water and melts at 176—178°C.

EXAMPLE 14

N-[4-(β-furoylaminoethyl)-benzenesulphonyl]-N'-isobutyl-urea

13.6 Grams of mercury chloride are dissolved in 120 ml of water and 50 ml of 2N-sodium hydroxide solution are added dropwise. To this mixture 16.5 grams of N - [4 - (β - furoylaminoethyl) - benzenesulphonyl] - N' - isobutyl - urea (melting point: 131—133°C; prepared from 4-(β-furoylaminoethyl)-benzenesulphonamide and isobutyl-mustard oil in the presence of potassium carbonate) dissolved in 80 ml of a mixture of equal parts of normal sodium hydroxide solution and dimethylformamide are added at about 40°C. The whole is stirred for 2½ hours at 40—50°C, the mercury sulphide formed is filtered with suction, the filtrate is clarified by means of charcoal and acidified with dilute hydrochloric acid. The N-[4-(β-furoylaminoethyl)-benzenesulphonyl]-N'-isobutyl-urea is filtered with suction and recrystallized from methanol. Melting point: 192—194°C.

EXAMPLE 15

N-[4-(β-furoylaminoethyl)-benzenesulphonyl]-N'-isobutyl-urea

4 Grams of N-[4-(β-furoylaminoethyl)-benzenesulphonyl]-N'-isobutyl-iso-urea methyl ether (in the form of an oil obtained by the reaction of N-[4-(β-furoylaminoethyl)-benzenesulphonyl]-N'-isobutyl-thiourea with mercury oxide in methanol) are heated on a steam bath together with 30 ml of concentrated hydrochloric acid until the formation of gas is terminated (about 10 minutes). The reaction mixture is cooled and diluted with water. The N-[4-(β-furoylaminoethyl)-benzenesulphonyl]-N'-isobutyl-urea is filtered with suction, and recrystallized from methanol. Melting point: 192—194°C.

EXAMPLE 16

N-[4-(pyridine-3-carbonamidomethyl)-benzenesulphonyl]-N'-cyclohexyl-urea

11.5 Grams of 4 - (pyridine - 3 - carbonamidomethyl) - benzenesulphonamide (melting point: 175°C; prepared from 4-aminomethyl-benzenesulphonamide and nicotic acid chloride-hydrochloride in pyridine) are suspended in 200 ml of acetone and dissolved by the addition of 1.75 grams of sodium hydroxide and water. 5.6 Grams of cyclohexyl isocyanate are dropped in while stirring at room temperature, and stirring is continued for 2 hours. The reaction mixture is filtered, the filtrate combined with water and hydrochloric acid, and the product is filtered with suction and recrystallized from a mixture of water and ethanol. The N-[4-(pyridine-3-carbonamidomethyl)-benzenesulphonyl]-N'-cyclohexyl-urea obtained melts at 200—202°C.

In an analogous manner there are obtained from 4-(β-pyridine-4-carbonamidomethyl)-benzenesulphonamide (melting point: 239—241°C):

- N - [4 - (β - pyridine - 4 - carbonamidoethyl) - benzenesulphonyl] - N' - (4 - methylcyclohexyl)-urea, melting at 187—188°C (from dimethylformamide/water), and
 N - [4 - (β - pyridine - 4 - carbonamidoethyl) - benzenesulphonyl] - N' - (4 - ethylcyclohexyl)-urea (trans-form), melting at 207—208°C;
 5 from 4 - (β - pyridine - 3 - carbonamidoethyl) - benzenesulphonamide (melting point: 205—206°C):
 N - [4 - (β - pyridine - 3 - carbonamidoethyl) - benzenesulphonyl] - N' - cyclohexyl-urea, melting at 184—185°C (from dimethylformamide/water);
 10 N - [4 - (β - pyridine - 3 - carbonamidoethyl) - benzenesulphonyl] - N' - (4 - methylcyclohexyl)-urea, melting at 123—124°C (from dimethylformamide/water), and
 N - [4 - (β - pyridine - 3 - carbonamidoethyl) - benzenesulphonyl] - N' - (4 - ethylcyclohexyl) - urea (trans - form), melting at 126—128°C (decomposition) (from methanol);
 15 from 4 - (β - β - pyridine - 3 - acrylamido } - ethyl) - benzenesulphonamide (melting point: 226—228°C):
 N - [4 - (β - β - pyridine - 3 - acrylamido } - ethyl) - benzenesulphonyl] - N' - (4-methyl-cyclohexyl)-urea (trans-form), melting at 194—196°C (from methanol).

EXAMPLE 17

- In a manner analogous to that described in Example 1 there is obtained the
 20 N - [4 - (β - furoylaminoethyl) - benzenesulphonyl] - N' - (Δ^3 - cyclohexenyl) - urea (melting point: 166—168°C) and the
 N - [4 - (β - thiophene - 2 - carbonamidoethyl) - benzenesulphonyl] - N' - (Δ^3 - cyclohexenyl)-urea (melting point: 181—183°C).
 In a manner analogous to that described in Example 2 there is obtained the
 25 N - [4 - (β - 5 - chloro - thiophene - 2 - carbonamidoethyl) - benzenesulphonyl] - N' - (Δ^3 - cyclohexenyl)-urea (melting point: 186—188°C).

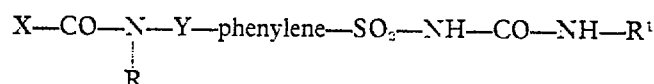
EXAMPLE 18

- In a manner analogous to that described in Example 3 there is obtained from
 4 - (β - { thiophene - 2 - acetamido } - ethyl) - benzenesulphonamide (melting point: 176—178°C)
 30 the N - [4 - (β - { thiophene - 2 - acetamido } - ethyl) - benzenesulphonyl] - N' - cyclohexyl-urea (melting point: 186°C) (from dimethylformamide/water) and
 the N - [4 - (β - { thiophene - 2 - acetamido } - ethyl) - benzenesulphonyl] - N' - (4-methylcyclohexyl)-urea (trans) (melting point: 173—174°C) from methanol/
 35 dimethylformamide);
 from 4 - (β - { 3 - phenyl - 4 - methylthiophene - 2 - carbonamido } - ethyl) - benzenesulphonamide (melting point: 183—185°C)
 the N - [4 - (β - { 3 - phenyl - 4 - methylthiophene - 2 - carbonamido } - ethyl) - benzenesulphonyl] - N' - cyclohexyl-urea (melting point: 150—152°C) (from
 40 methanol) and
 the N - [4 - (β - { 3 - phenyl - 4 - methylthiophene - 2 - carbonamido } - ethyl) - benzenesulphonyl] - N' - (4-methyl-cyclohexyl)-urea (trans) (melting point: 136—138°C; (from methanol);
 from 4 - (3 - methylthiophene - 2 - carbonamidomethyl) - benzenesulphonamide
 45 (melting point 153°C)
 the N - [4 - (3 - methylthiophene - 2 - carbonamidomethyl) - benzenesulphonyl] - N' - cyclohexyl-urea (melting point: 163—165°C) (from methanol) and
 the N - [4 - (3 - methylthiophene - 2 - carbonamidomethyl) - benzenesulphonyl] - N' - (4-methylcyclohexyl)-urea (trans) (melting point: 190—191°C) (from
 50 methanol);
 from 4 - (β - { N - methyl - 3 - methoxythiophene - 2 - carbonamido } - ethyl) - benzenesulphonamide (melting point: 132—134°C)
 the N - [4 - (β - { N - methyl - 3 - methoxythiophene - 2 - carbonamido } - ethyl) - benzenesulphonyl] - N' - cyclohexyl-urea (melting point: 143—145°C) (from
 55 methanol) and
 the N - [4 - (β - { N - methyl - 3 - methoxythiophene - 2 - carbonamido } - ethyl) - benzenesulphonyl] - N' - (4-methylcyclohexyl)-urea (trans) (melting point 159—161°C (from methanol);
 from 4 - (β - { 3,4 - tetramethylene - thiophene - 2 - carbonamido } - ethyl - benzene-
 60 sulphonamide (melting point: 173—174°C)
 the N - [4 - (β - { 3,4 - tetramethylene - thiophene - 2 - carbonamido } - ethyl) - benzenesulphonyl] - N' - cyclohexylurea (melting point 192—194°C (from dimethylformamide/water) and

- the N - [4 - (β - {3,4 - tetramethylene - thiophene - 2 - carbonamido} - ethyl)-benzenesulphonyl] - N'-(4-methylcyclohexyl) - urea (trans) (melting point: 127—129°C) (from methanol);
- 5 from 4 - (3,4 - tetramethylene - thiophene - 2 - carbonamidomethyl) - benzene-sulphonamide (melting point: 174—175°C)
- the N - [4 - (3,4 - tetramethylene - thiophene - 2 - carbonamido - methyl) - benzene-sulphonyl] - N'-(4-methylcyclohexyl)-urea (trans) (melting point: 192—193°C) (from methanol);
- 10 from 4 - (β - {thiophene - (3) - oxyacetamido} - ethyl) - benzenesulphonamide (melting point: 203°C)
- the N - [4 - (β - {thiophene - (3) - oxyacetamido} - ethyl) - benzenesulphonyl] - N'-cyclohexyl-urea (melting point: 148—149°C) (from methanol) and
- the N - [4 - (β - {thiophene - (3) - oxyacetamido} - ethyl) - benzenesulphonyl] - N'-(4-methylcyclohexyl)-urea (trans), (melting point: 182—183°C) (from methanol);
- 15 from 4 - (β - {3 - methoxymethoxy - thiophene - 2 - carbonamido} - ethyl) - benzene-sulphonamide (melting point: 160—162°C)
- the N - [4 - (β - {3 - methoxymethoxy - thiophene - 2 - carbonamido} - ethyl)-benzenesulphonyl] - N'-(4-methylcyclohexyl)-urea (trans) (melting point: 163—165°C) (from methanol);
- 20 from 4 - (β - {3 - methoxyethoxy - thiophene - 2 - carbonamido} - ethyl) - benzene-sulphonamide (melting point: 132—134°C)
- the N - [4 - (β - {3 - methoxyethoxy - thiophene - 2 - carbonamido} - ethyl)-benzenesulphonyl] - N'-cyclohexyl-urea (melting point: 135—137°C) (from methanol) and
- 25 the N - [4 - (β - {3 - methoxyethoxy - thiophene - 2 - carbonamido} - ethyl)-benzenesulphonyl] - N'-(4-methylcyclohexyl)-urea (trans) (melting point: 103—105°C) (from methanol);
- 30 from 4 - (β - {3 - allyloxythiophene - 2 - carbonamido} - ethyl) - benzenesulphonamide (melting point: 145—147°C)
- the N - [4 - (β - {3 - allyloxythiophene - 2 - carbonamido} - ethyl) - benzene-sulphonyl] - N'-(4-methylcyclohexyl)-urea (trans) (melting point: 135—136°C) (from methanol).

WHAT WE CLAIM IS:—

- 35 1. Benzenesulphonyl-ureas of the general formula



in which

R represents hydrogen, lower alkyl or lower phenylalkyl,

R¹ represents

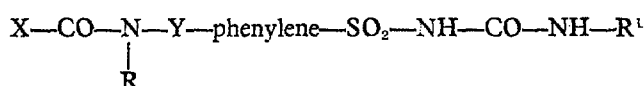
- 40 a) alkyl, alkenyl or mercaptoalkyl of 2 to 8 carbon atoms,
- b) alkoxyalkyl, alkylmercaptoalkyl or alkylsulphinylalkyl of 4 to 8 carbon atoms each, at least two of which carbon atoms form the alkylene portion of the alkoxyalkyl, alkylmercaptoalkyl or alkylsulphinylalkyl,
- 45 c) phenyl-lower alkyl or phenylcyclopropyl,
- d) cyclohexyl-lower alkyl, cycloheptylmethyl, cycloheptylethyl or cyclooctyl-methyl,
- e) endoalkylene-cyclohexyl, endoalkylene-cyclohexenyl, endoalkylene-cyclohexyl-methyl or endoalkylene-cyclohexenylmethyl, each containing 1 or 2 endo-alkylene carbon atoms,
- 50 f) lower alkylcyclohexyl or lower alkoxycyclohexyl,
- g) cycloalkyl of 5 to 8 carbon atoms,
- h) cyclohexenyl or cyclohexenylmethyl,
- i) a heterocyclic ring of 4 or 5 carbon atoms, 1 oxygen or sulphur atom and which may also contain up to 2 ethylenic double linkages, or
- 55 k) a heterocyclic ring linked to the nitrogen atom by means of a methylene group and containing 4 or 5 carbon atoms and 1 oxygen atom or 1 sulphur atom and which may also contain up to 2 ethylenic double linkages,
- X represents
- 60 a) thiophenyl or thiophenoxy which may contain 1 or 2 substituents selected from halogen atoms, lower alkyl, lower alkoxy, lower alkenyloxy, lower alkoxy-lower alkoxy, lower phenalkoxy and aryl groups, and a polymethylene chain of 3 or 4 carbon atoms linked by both ends to the thiophenyl nucleus,



- the N - [4 - (β - {3,4 - tetramethylene - thiophene - 2 - carbonamido} - ethyl)-
benzenesulphonyl] - N'-(4-methylcyclohexyl) - urea (trans) (melting point: 127—
129°C) (from methanol);
- 5 from 4 - (3,4 - tetramethylene - thiophene - 2 - carbonamidomethyl) - benzene-
sulphonamide (melting point: 174—175°C)
- the N - [4 - (3,4 - tetramethylene - thiophene - 2 - carbonamido - methyl) - benzene-
sulphonyl]-N'-(4-methylcyclohexyl)-urea (trans) (melting point: 192—193°C)
(from methanol);
- 10 from 4 - (β - {thiophene - (3) - oxyacetamido} - ethyl) - benzenesulphonamide
(melting point: 203°C)
- the N - [4 - (β - {thiophene - (3) - oxyacetamido} - ethyl) - benzenesulphonyl]-
N'-cyclohexyl-urea (melting point: 148—149°C) (from methanol) and
- the N - [4 - (β - {thiophene - (3) - oxyacetamido} - ethyl) - benzenesulphonyl]-
N'-(4-methylcyclohexyl)-urea (trans), (melting point: 182—183°C) (from
15 methanol);
- from 4 - (β - {3 - methoxymethoxy - thiophene - 2 - carbonamido} - ethyl) - benzene-
sulphonamide (melting point: 160—162°C)
- the N - [4 - (β - {3 - methoxymethoxy - thiophene - 2 - carbonamido} - ethyl)-
benzenesulphonyl]-N'-(4-methylcyclohexyl)-urea (trans) (melting point: 163—
20 165°C) (from methanol);
- from 4 - (β - {3 - methoxyethoxy - thiophene - 2 - carbonamido} - ethyl) - benzene-
sulphonamide (melting point: 132—134°C)
- the N - [4 - (β - {3 - methoxyethoxy - thiophene - 2 - carbonamido} - ethyl)-
benzenesulphonyl]-N'-cyclohexyl-urea (melting point: 135—137°C) (from
25 methanol) and
- the N - [4 - (β - {3 - β - methoxyethoxy - thiophene - 2 - carbonamido} - ethyl)-
benzenesulphonyl]-N'-(4-methylcyclohexyl)-urea (trans) (melting point: 103—
105°C) (from methanol);
- 30 from 4 - (β - {3 - allyloxythiophene - 2 - carbonamido} - ethyl) - benzenesulphon-
amide (melting point: 145—147°C)
- the N - [4 - (β - {3 - allyloxythiophene - 2 - carbonamido} - ethyl) - benzene-
sulphonyl]-N'-(4-methylcyclohexyl)-urea (trans) (melting point: 135—136°C)
(from methanol).

WHAT WE CLAIM IS:—

1. Benzenesulphonyl-ureas of the general formula



in which

R represents hydrogen, lower alkyl or lower phenylalkyl,

R¹ represents

- 40 a) alkyl, alkenyl or mercaptoalkyl of 2 to 8 carbon atoms,
- b) alkoxyalkyl, alkylmercaptoalkyl or alkylsulphinylalkyl of 4 to 8 carbon atoms
each, at least two of which carbon atoms form the alkylene portion of the
alkoxyalkyl, alkylmercaptoalkyl or alkylsulphinylalkyl,
- 45 c) phenyl-lower alkyl or phenylcyclopropyl,
- d) cyclohexyl-lower alkyl, cycloheptylmethyl, cycloheptylethyl or cyclooctyl-
methyl,
- e) endoalkylene-cyclohexyl, endoalkylene-cyclohexenyl, endoalkylene-cyclohexyl-
methyl or endoalkylene-cyclohexenylmethyl, each containing 1 or 2 endo-
alkylene carbon atoms,
- 50 f) lower alkylcyclohexyl or lower alkoxycyclohexyl,
- g) cycloalkyl of 5 to 8 carbon atoms,
- h) cyclohexenyl or cyclohexenylmethyl,
- i) a heterocyclic ring of 4 or 5 carbon atoms, 1 oxygen or sulphur atom and
which may also contain up to 2 ethylenic double linkages, or
- 55 k) a heterocyclic ring linked to the nitrogen atom by means of a methylene group
and containing 4 or 5 carbon atoms and 1 oxygen atom or 1 sulphur atom
and which may also contain up to 2 ethylenic double linkages,

X represents

- 60 a) thiophenyl or thiophenoxy which may contain 1 or 2 substituents selected
from halogen atoms, lower alkyl, lower alkoxy, lower alkenyloxy, lower alkoxy-
lower alkoxy, lower phenalkoxy and aryl groups, and a polymethylene chain
of 3 or 4 carbon atoms linked by both ends to the thiophenyl nucleus,

b) furyl which may contain 1 or 2 substituents selected from halogen atoms and methyl groups,

c) pyridyl which may contain 1 or 2 substituents selected from halogen atoms and lower alkyl groups,

the heterocyclic ring system mentioned under (a), (b) or (c) being linked either directly or by means of a hydrocarbon chain of 1 or 2 carbon atoms to the adjacent carbonyl group, and

Y represents a hydrocarbon chain of 1 to 4 carbon atoms.

2. Physiologically tolerable salts of any one of the compounds claimed in claim 1.

3. Benzenesulphonyl-ureas of the general formula given in claim 1 in which

R is hydrogen,

R₁ is (a) alkyl of 3 to 6 carbon atoms,

(b) phenyl-lower alkyl,

(c) cyclohexyl-lower alkyl,

(d) endoalkylene-cyclohexyl, endoalkylene-cyclohexenyl, endoalkylene-cyclohexyl-methyl or endoalkylene-cyclohexenyl-methyl, each containing 1 or 2 endoalkylene carbon atoms,

(e) lower alkyl-cyclohexyl or lower alkoxy-cyclohexyl,

(f) cycloalkyl of 5 to 8 carbon atoms, or

(g) cyclohexenyl or cyclohexenyl methyl,

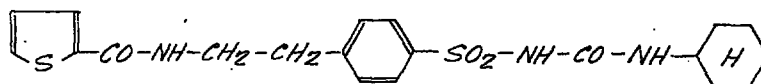
X is (a) thiophenyl which may contain 1 or 2 substituents selected from halogen atoms, lower alkyl, lower alkoxy, lower alkenyloxy, lower alkoxy-lower alkoxy, phenyl-lower alkoxy and aryl groups, and a polymethylene chain of 4 carbon atoms linked by both ends to the thiophenyl nucleus, or

(b) furyl which may contain one halogen substituent,

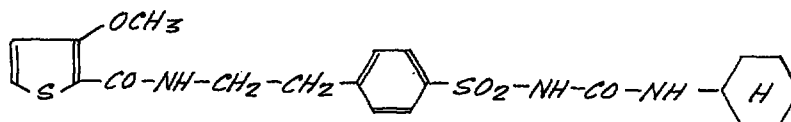
Y is a hydrocarbon chain of 2 or 3 carbon atoms, and phenylene is unsubstituted *p*-phenylene.

4. Physiologically tolerable salts of any one of the compounds claimed in claim 3.

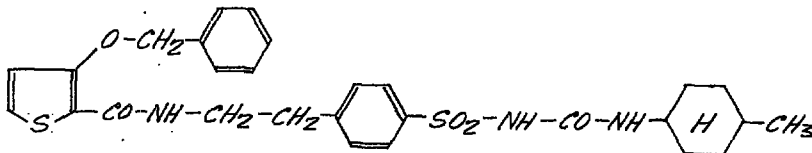
5. N - [4 - (β - thiophene - 2 - carbonamidoethyl) - benzenesulphonyl] - N'-cyclohexyl-urea of the formula



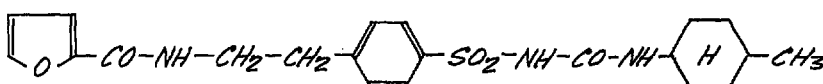
6. N - [4 - (β - methoxythiophene - 2 - carbonamidoethyl) - benzenesulphonyl] - N'-cyclohexyl-urea of the formula



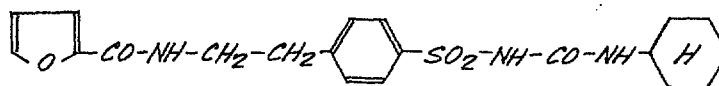
7. N - [4 - (β - benzyloxythiophene - 2 - carbonamidoethyl) - benzenesulphonyl] - N'-(4-methylcyclohexyl)-urea of the formula



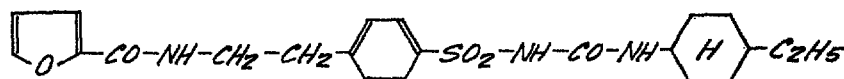
8. N - [4 - (β - furoylaminoethyl) - benzenesulphonyl] - N' - (4 - methyl-cyclohexyl)-urea of the formula



9. N - [4 - (β - furoylaminoethyl) - benzenesulphonyl] - N' - cyclohexyl - urea of the formula



5 10. N - [4 - (β - furoylaminoethyl) - benzenesulphonyl] - N' - (4 - ethyl-cyclohexyl)-urea of the formula 5



11. Any one of the benzenesulphonyl-ureas as claimed in claim 1 that is specifically described in any one of the Examples herein, other than the compounds claimed in claims 5 to 10.

10 12. Physiologically tolerable salts of any one of the compounds claimed in any one of claims 5 to 11. 10

13. A pharmaceutical preparation for oral administration and lowering the blood sugar level in the treatment of diabetes mellitus, which comprises a compound as claimed in any one of claims 1 to 4 in admixture or conjunction with a pharmaceutically suitable carrier. 15

14. A pharmaceutical preparation for oral administration and lowering the blood sugar level in the treatment of diabetes mellitus, which comprises a compound as claimed in any one of claims 5 to 12 in admixture or conjunction with a pharmaceutically suitable carrier. 15

20 15. A pharmaceutical preparation as claimed in claim 13 or claim 14, which is in the form of a tablet. 20

16. A pharmaceutical preparation as claimed in any one of claims 13 to 15, which contains in dosage unit form from 0.5 to 100 milligrams of the active ingredient.

25 17. A pharmaceutical preparation as claimed in claim 16, which contains in dosage unit form from 2 to 10 milligrams of the active ingredient. 25

18. A process for the manufacture of benzenesulphonyl-urea of the general formula given in claim 1, conducted substantially as hereinbefore described.

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

