

1122919



PATENT SPECIFICATION

NO DRAWINGS

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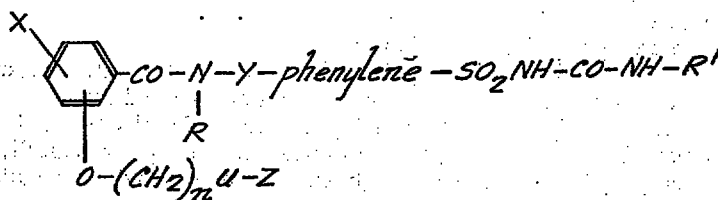
Int. Cl.:—C 07 c 143/82

COMPLETE SPECIFICATION

Benzenesulphonyl-Ureas and process for preparing them

We, FARBWERKE HOECHST AKTIENGESELLSCHAFT, Vormalig Meister Lucius & Brüning, a Company recognized 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 corresponding to the general formula



in which:

R represents a hydrogen atom or a lower alkyl or lower phenylalkyl radical,

R¹ represents:

- an alkyl, alkenyl or mercaptoalkyl radical containing 2 to 8 carbon atoms,
- an alkoxyalkyl, alkylmercaptoalkyl or alkylsulphinyllalkyl radical containing 4 to 8 carbon atoms of which at least two belong to the alkylene part of the alkoxyalkyl, alkylmercaptoalkyl or alkylsulphinyllalkyl radical,
- a lower phenylalkyl or phenylcyclopropyl radical,
- a lower cyclohexyl-alkyl, cycloheptylmethyl, cycloheptylethyl or cyclo-octylmethyl radical,
- an endoalkylene-cyclohexyl, endoalkylene-cyclohexenyl, endoalkylene-cyclohexylmethyl or endoalkylene-cyclohexenylmethyl radical containing 1 or 2 endoalkylene-carbon atoms,
- a lower alkylcyclohexyl or lower alkoxy-cyclohexyl radical,
- a cycloalkyl radical containing 5 to 8 carbon atoms,
- a cyclohexenyl or cyclohexenylmethyl radical,
- a heterocyclic ring containing 4 or 5 carbon atoms and one oxygen or sulphur atom as well as up to two ethylenic double bonds, or
- a heterocyclic ring containing 4 or 5 carbon atoms and one oxygen or sulphur atom, linked to the nitrogen atom by means of a methylene radical and in addition containing up to two ethylenic double bonds;

"phenylene" represents a phenylene group which may be unsubstituted or may be substituted by one or more substituents selected from halogen atoms, and lower alkyl and lower alkoxy groups

X represents a hydrogen or halogen atom or a lower alkyl, lower alkoxy, trifluoromethyl or nitro group,

Y represents a hydrocarbon chain containing 1 to 4 carbon atoms,

n represents 1, 2 or 3,

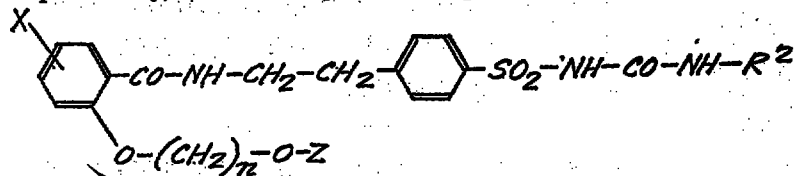
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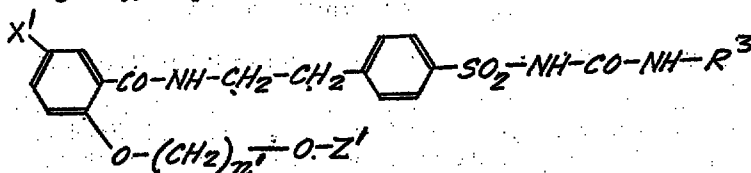
U represents oxygen or sulphur, and

Z represents a saturated or unsaturated, aliphatic or cycloaliphatic hydrocarbon radical containing up to 6 carbon atoms, a phenyl or a benzyl radical; the group $-O-(CH_2)_n-U-Z$ being preferably in 2-position and X being preferably in 4- or 5-position.

More particularly, the invention provides compounds of the formula



wherein X, n and Z have the meanings given above and R² is a cyclohexyl or lower alkyl-cyclohexyl radical, and, advantageously, compounds of the formula



wherein

R³ represents a cyclohexyl, 4-methyl-cyclohexyl, or 4-ethyl cyclohexyl group.

X¹ represents a hydrogen, chlorine or fluorine atom, or a methyl or methoxy group,

n¹ represents 1 or 2,

Z¹ represents a methyl or ethyl group.

In the above and the following definitions "lower alkyl" always stands for an alkyl group containing 1 to 4 carbon atoms in a straight or branched chain.

The invention also includes physiologically tolerable salts of the above compounds. The compounds of the above general formula and their physiologically tolerable salts are new compounds which show hypoglycemic properties and, above all, a long lasting hypoglycemic action.

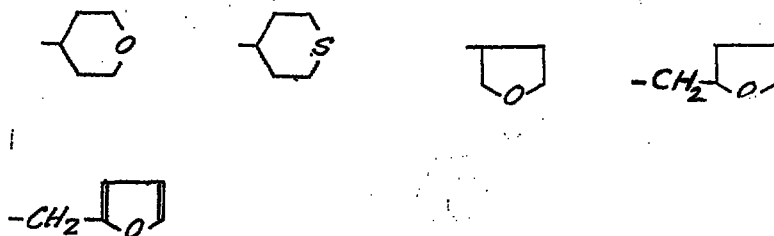
According to the above-mentioned definitions R may represent, for instance, a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, benzyl, α - or β -phenyl-ethyl, α -, β - or γ -phenylpropyl group. Compounds in which R stands for a methyl or benzyl group and particularly those in which R represents a hydrogen atom are preferred.

R¹ may represent, for instance, an ethyl, propyl, isopropyl, butyl, isobutyl, secondary butyl, straight-chained or branched amyl (pentyl), hexyl, heptyl or octyl group; the radicals containing one ethylenic double bond corresponding to the above-mentioned hydrocarbon radicals, for instance, allyl or crotyl, furthermore alkyl radicals containing 2 to 8 carbon atoms and carrying a mercapto group, such, for instance, as β -mercaptoethyl or higher mercapto alkyls. Furthermore, R¹ may represent, for instance γ -methoxy-propyl, δ -methoxy-n-butyl, β -ethoxyethyl, γ -ethoxy-propyl, δ -ethoxy-butyl or higher alkoxy-ethyls, alkoxy-propyls or alkoxy-butyls as well as the corresponding groups which instead of the oxygen atom contain a sulphur atom or the sulphanyl group. There may likewise be mentioned as R¹: benzyl, α -phenyl-ethyl, β -phenyl-ethyl, α -, β - or γ -phenylpropyl or phenylbutyls.

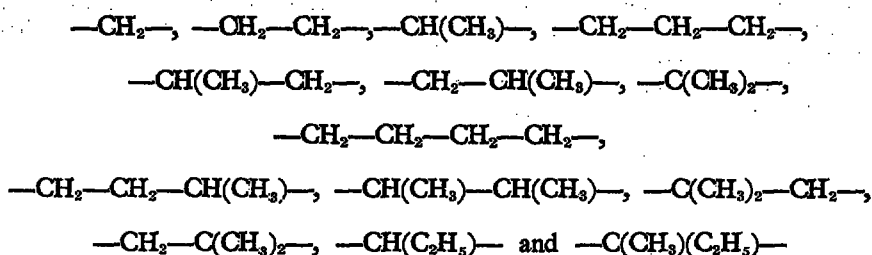
Particularly preferred are compounds which as R¹ contain a cycloaliphatic hydrocarbon radical which may be substituted by an alkyl or alkoxy group or bound by alkylene to the nitrogen atom. As radicals of said type, there may be mentioned, for example, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, methylcyclohexyl, ethylcyclohexyl, propylcyclohexyl, isopropylcyclohexyl, methoxy-cyclohexyl, ethoxy-cyclohexyl, propoxy-cyclohexyl and isopropoxy-cyclohexyl, the alkyl or alkoxy groups being in 2- or 3-position and, preferably, in 4-position, in cis- as well as in trans-position; cyclohexylmethyl, α - or β -cyclohexylethyl, cyclohexyl-propyls, 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 cis-form as well as in trans-form.

Finally, there are suitable as R¹ heterocyclic rings which contain in addition

to 4 to 5 carbon atoms one oxygen or sulphur atom and up to 2 double linkages and which may be linked to the adjacent nitrogen atom by a methylene group. Examples of heterocyclic rings of this kind are



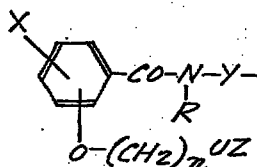
5 As examples of the bridge member Y there may be mentioned:



The phenylene group designated in the formula as "phenylene" is preferably unsubstituted. It can, however, contain one or more substituents selected from halogen atoms and lower alkyl and lower alkoxy groups. It may carry the remaining parts of the molecule in ortho-, meta- or para-position to each other, the para-position being preferred.

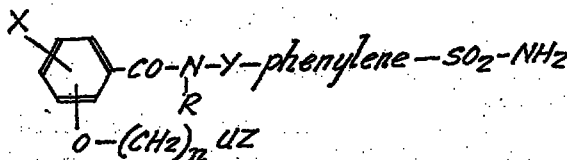
The present invention also provides a process for the manufacture of compounds of the above general formula, wherein

a) a benzenesulphonyl-isocyanate, benzenesulphonyl-carbamic acid ester, benzenesulphonyl-thiocarbamic acid ester, benzenesulphonyl-carbamic acid halide or benzenesulphonyl urea substituted by the group



in which R, U, X, Y and Z and n have the meanings given above is reacted with an R^1 -substituted amine or a salt thereof, in which R^1 has the meaning given above;

b) a benzenesulphonamide of the formula

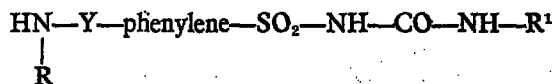


or a salt thereof is reacted with an R^1 -substituted isocyanate, carbamic acid ester, thiocarbamic acid ester, carbamic acid halide or urea, R, R^1 , U, X, Y and Z having the meanings given above:

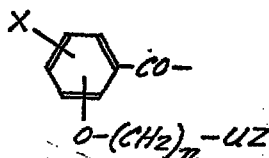
c) a correspondingly substituted benzenesulphonyl-halide is reacted with an R^1 -substituted urea, isourea ether, isothiurea ether or parabanic acid and the benzenesulphonyl-isourea ether, benzenesulphonyl-isothiurea ether or benzenesulphonyl-parabanic acid obtainable in this way is hydrolyzed;

d) in a correspondingly substituted benzenesulphonyl-thiourea the sulphur atom is exchanged in known manner for an oxygen atom,

- e) a corresponding benzenesulphonyl-urea or benzenesulphenyl-urea is oxidised or
f) in a benzenesulphonyl-urea of the formula

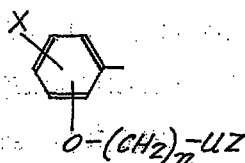


the radical



is introduced by acylation, if desired in several stages, and if desired the reaction product is treated with an alkaline agent to form a salt, R, R¹, U, X, Y and Z having the meanings given above.

According to the nature of the member



one or other of the methods mentioned above may, in the case of certain individual compounds corresponding to the general formula, be unsuitable. Such cases which do not occur very often can easily be recognized by the expert and there will be no difficulty in applying in these cases one of the other methods of synthesis described above.

Instead of the benzenesulphonyl-isocyanates there can likewise be used reaction products of a benzenesulphonyl-isocyanate with an acid amide such, for example, as caprolactam or butyrolactam, furthermore with a weakly basic amine such, for example, as carbazoles.

The above-mentioned benzenesulphonyl-carbamic acid esters or the benzenesulphonyl-thiocarbamic acid esters may contain in the alcohol component a low-molecular alkyl group or a phenyl group. The same applies to the R¹-substituted carbamic acid esters or the corresponding monothio-carbamic acid esters. The term low-molecular or lower alkyl group is used herein in all cases to mean an alkyl group containing not more than 4 carbon atoms.

As carbamic acid halides there are suitable, above all, the chlorides.

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

Furthermore, it is possible to start from ureas of the formula R¹-NH-CO-NH₂ or acylated ureas of the formula R¹-NH-CO-NH-acyl, wherein acyl preferably represents a low-molecular aliphatic or aromatic acid radical or the nitro group, or from phenyl-ureas of the formula R¹-NH-CO-NH-C₆H₅, or from diphenyl-ureas of the formula R¹-NH-CO-N(C₆H₅)₂. The phenyl groups can be substituted or linked to each other directly or likewise by means of a bridge member such as -CH₂-, -NH-, -O- or -S-. It is likewise possible to start from an N,N'-di-substituted urea of the formula R¹-NH-CO-NH-R¹ and to react it with a correspondingly substituted benzenesulphonamide.

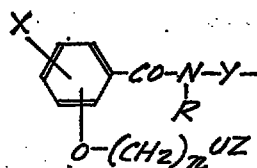
The sulphur atom in correspondingly substituted benzenesulphonyl-thio-ureas can be replaced by an oxygen atom, for instance, with the aid of an oxide or salt of a heavy metal or likewise by treatment with an oxidizing agent such, for example, as hydrogen peroxide, sodium peroxide or nitrous acid.

Thioureas may likewise be desulphurized by treating them with phosgene or phosphorus pentachloride. Chloroformic acid amidines or chloroformic acid carbodiimides obtained as intermediate products can be converted into the benzenesulphonylureas by suitable processes such, for instance, as saponification or addition of water.

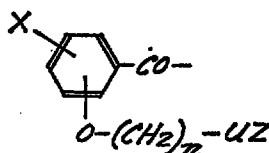
In the process of the invention isothiurea-ethers are considered equivalents to thioureas as starting substances for the desulphurization and react in a similar way.

Generally, the methods of carrying out the aforesaid processes may vary within wide limits as regards the reaction conditions, and they may be adapted to each individual case. The reactions may be carried out, for example, by using solvents, at room temperature or at an elevated temperature.

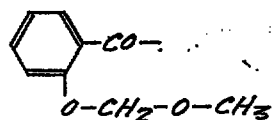
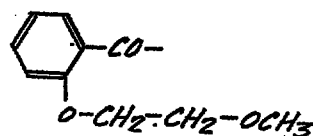
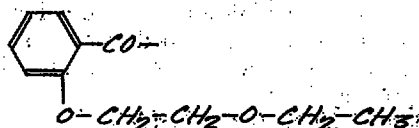
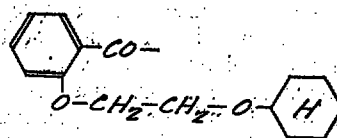
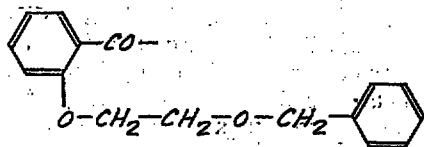
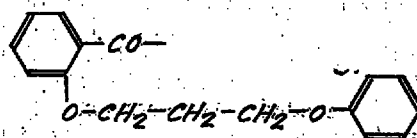
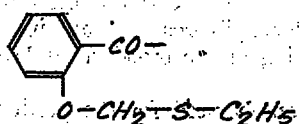
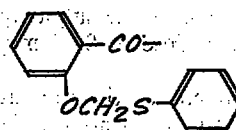
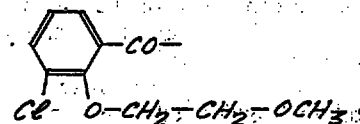
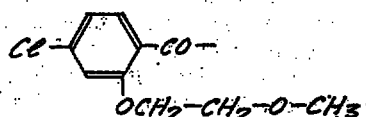
As starting materials there are used on the one hand compounds containing a benzene radical substituted by the group

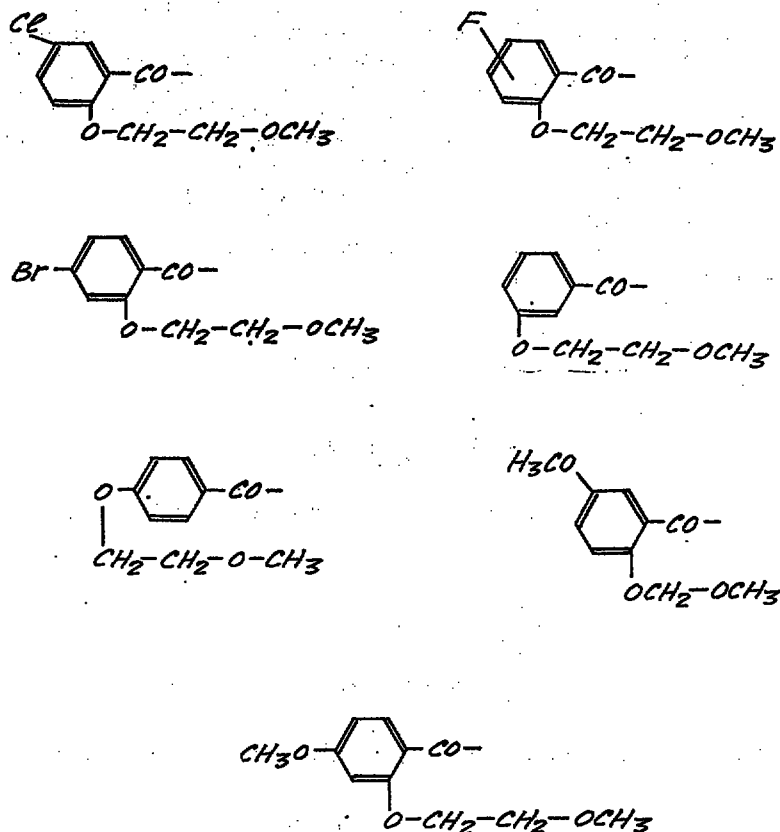


in which R, U, X, Y and Z have the meaning given above. As examples for the component



of this formula there may be mentioned, for example, the following compounds:





The blood sugar lowering action of the benzenesulphonyl-urea derivatives described above can be ascertained, for example, in rabbits by administering to the animal the product of the invention in a dose of 10 milligrams/kilogram of body weight and by determining the blood sugar value according to the known method of Hagedorn-Jensen or by means of an auto-analyser over a prolonged period.

It has been found, for example, that a dose of 10 mg/kg of N-[4-(β -<2-methoxy-methoxybenzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl urea causes a lowering of the blood sugar level of 19% after 3 hours which after 24 hours even attains 33% and falls to zero only after a period of 48 hours. By administration of 10 milligrams of N-[4-(β -<2- β -methoxyethoxy-benzamido>-ethyl)-benzenesulphonyl]-N'-(4-methylcyclohexyl)-urea the blood sugar level is reduced after 3 hours by 31% and after a period of 24 hours the reduction still amounts to 20%; whereas the known N-[4-methyl-benzenesulphonyl]-N'-butyl-urea in a dose of less than 25 mg/kg does not cause a lowering of the blood sugar level in rabbits.

The high efficiency of the above-described benzenesulphonyl-ureas becomes particularly obvious if the dose is further reduced. If the N-[4-(β -<2-methoxymethoxy-benzamido>-ethyl)-benzene-sulphonyl]-N'-(4-methylcyclohexyl)-urea is administered to the rabbit in a dose of 0.05 mg/kg a distinct lowering of the blood sugar level is still observed.

The compounds of the present invention are preferably used for the production of pharmaceutical preparations. Accordingly the present invention also provides a pharmaceutical preparation for oral administration and lowering the blood sugar level in the treatment of diabetes mellitus, which comprises a compound of the invention in admixture or conjunction with a pharmaceutically suitable carrier. The compounds can be used as such or in the form of their physiologically tolerable salts or in the presence of substances causing salt formation. For the salt formation there may be used: alkaline agents such, for example, as alkali metal hydroxides, alkaline earth metal hydroxides, alkali metal carbonates or alkaline earth metal carbonates, alkali metal

bicarbonates or alkaline earth metal bicarbonates.

The pharmaceutical preparations are preferably made up in the form of tablets containing in addition to the products of the present invention the usual adjuvants and carrier substances such, for example, as talc, starch, lactose, tragacanth or magnesium stearate.

A preparation containing one of the benzenesulphonyl-ureas of the present invention as active substance, for example, a tablet or a powder, with or without the afore-said additives is preferably formed into a suitable unit dosage form. The dose chosen should take into consideration the activity of the benzenesulphonyl-urea used and the desired effect. Advantageously the dosage per unit amounts to about 0.5 to 100 milligrams, preferably 2 to 10 milligrams, but considerably higher or lower dosage units can also be used which, if desired, are divided or multiplied prior to administration.

The following examples illustrate the invention:

EXAMPLE 1.

N-[4-(β-(2-methoxy-ethoxy-benzamido)-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea.

a) 2.6 Grams of N - [4 - (β - (2 - methoxy - ethoxy - benzamido) - ethyl)-benzenesulphonyl] - N' - cyclohexyl - thio - urea (prepared from N - (4 - β - (2-methoxy - ethoxy - benzamido) - ethyl) - benzenesulphonamide and cyclohexyl-mustard oil, melting point 116—118°C) are dissolved in about 20 millilitres of 2N-sodium hydroxide solution. 5 Grams of H₂O₂ of 35% strength are added whereby strong heating is caused. Upon standing for some time the solution is cooled and acidified by means of dilute acetic acid. The precipitate obtained, i.e. the N-[4-(β-(2-methoxy-ethoxy-benzamido)-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea is filtered off with suction and recrystallized from methanol. Melting point 160—162°C.

b) 2.6 Grams of N - [4 - (β - (2 - methoxy - ethoxy - benzamido) - ethyl)-benzenesulphonyl] - N' - cyclohexyl - thio - urea are dissolved in 30 millilitres of methanol. After addition of methyl iodide in a slight excess the solution is heated for 45 minutes on the steam bath with reflux. After elimination by distillation of methanol and excessive methyl-iodide there remains an oily residue of N-[4-(β-(2-methoxy-ethoxy-benzamido)-ethyl)-benzenesulphonyl]-N'-cyclohexyl-isothio-urea methyl ether which is dissolved in 5 millilitres of dioxane and to which 10 millilitres of 2N-sodium hydroxide solution are added. After having been heated for 1 hour on the steam bath, the solution is poured into water and acidified. After having been filtered with suction and recrystallized from methanol the precipitate of N-[4-(β-(2-methoxy-ethoxy-benzamido)-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea obtained melts at 160—162°C.

c) 2.6 Grams of N - [4 - (β - (2 - methoxy - ethoxy - benzamido) - ethyl)-benzenesulphonyl] - N' - cyclohexyl - thio - urea are dissolved in 50 millilitres of methanol. 1.1 Gram of HgO and a small amount of K₂CO₃ are added and the whole is heated with stirring for 5 hours and 30 minutes to 45°C. After elimination by filtration of the HgS formed the solution is concentrated under reduced pressure. An oily residue of N - [4 - (β - (2 - methoxy - ethoxy - benzamino) - ethyl) - benzenesulphonyl] - N' - cyclohexyl - isourea - methylether is obtained which is dissolved in about 5 millilitres of dioxane. About 10 millilitres of 2N-sodium hydroxide solution are added and the substance is heated for 1 hour on the steam bath. It is then poured into water and acidified. The precipitate of N-[4-(β-(2-methoxy-ethoxy-benzamido)-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea is filtered off with suction and recrystallized from dilute methanol. Melting point 160—162°C.

EXAMPLE 2.

N-[4-(β-(2-methoxy-methoxy-benzamido)-ethyl)-benzenesulphonyl]-N'-(4-methylcyclohexyl)-urea (trans).

9.1 Grams of 4 - (β - (2 - methoxy - methoxy - benzamido) - ethyl) - benzenesulphonamide (melting point 169—170°C) are dissolved in 12.5 millilitres of 2N-sodium hydroxide solution and 30 millilitres of acetone and while stirring at 0—5°C 3.6 grams of trans-4-methylcyclohexyl-isocyanate are dropwise added. Stirring is continued for a further 3 hours, water and methanol are added and any undissolved matter is filtered off, and the filtrate is acidified with dilute acetic acid. After recrystallization from methanol the N - [4 - (β - (2 - methoxymethoxy - benzamido) - ethyl) - ben-

- zene - sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans) obtained in crystalline form melts at 162—163°C. In an analogous manner there are obtained:
- (a) N - [4 - (β - <2 - methoxymethoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl-urea, melting point 152—154°C (from methanol);
- 5 (b) N - [4 - (β - <4 - methoxymethoxy - benzamido> - ethyl) - benzenesulphonamide, (melting point 196—197°C) there are obtained:—
- (b) N - [4 - (β - <4 - methoxymethoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl-urea, melting point: 175—176°C (from methanol/dimethylformamide); and
- 10 (c) N - [4 - (β - <4 - methoxymethoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - (4-methylcyclohexyl) - urea (trans), melting point 180—181°C (from methanol/dimethylformamide);
- from 4 - (β - <3 - β - methoxyethoxy - benzamido> - ethyl) - benzenesulphonamide (melting point 134—136°C);
- 15 (d) N - [4 - β - <3 - β - methoxyethoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl-urea, melting point 132—133°C (from methanol), and
- (e) N - [4 - (β - <3 - β - methoxyethoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - (4-methylcyclohexyl) - urea (trans), melting point 157—159°C (from methanol);
- from 4 - (β - <4 - β - methoxyethoxy - benzamido> - ethyl) - benzenesulphonamide (melting point 212—214°C):—
- 20 (f) N - [4 - (β - <4 - β - methoxyethoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea, melting point: 200—201°C (from methanol/dimethylformamide);
- (g) N - [4 - (β - <4 - β - methoxyethoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - butyl - urea, melting point 197—198°C (from methanol/dimethylformamide) and
- 25 (h) N - [4 - (β - <4 - β - methoxyethoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 208—209°C (from methanol/dimethylformamide);
- from 4 - (β - <2 - γ - phenoxypropoxy - benzamido> - ethyl) - benzenesulphonamide (melting point 168—170°C):—
- 30 (i) N - [4 - (β - <2 - γ - phenoxypropoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl-urea, melting point 148—149°C (from methanol),
- (j) N - [4 - (β - <2 - γ - phenoxypropoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - butyl - urea, melting point 142—144°C (from methanol/dimethylformamide) and
- 35 (k) N - [4 - (β - <2 - γ - phenoxypropoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methylcyclohexyl) - urea (trans), melting point 169—170°C (from methanol);
- from 4 - (β - <2 - phenylmercaptomethoxy - benzamido> - ethyl) - benzenesulphonamide (melting point 152—153°C):—
- 40 (l) N - [4 - (β - <2 - phenylmercaptomethoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea, melting point 136—138°C (from methanol);
- from 4 - (β - <2 - β - methoxyethoxy - 5 - methyl - benzamido> - ethyl) - benzenesulphonamide (melting point 156—158°C):—
- 45 (m) N - [4 - (β - <2 - β - methoxyethoxy - 5 - methyl - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea, melting point 161—163°C (from methanol) and
- (n) N - [4 - (β - <2 - β - methoxyethoxy - 5 - methyl - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methylcyclohexyl) - urea (trans), melting point 157—158°C (from methanol);
- from 4 - (β - <2 - β - methoxyethoxy - 5 - chloro - benzamido> - benzenesulphonamide, (melting point 161—162°C):—
- 50 (o) N - [4 - (β - <2 - β - methoxyethyl - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea, melting point 151—153°C (from methanol) and
- 55 (p) N - [4 - (β - <2 - β - methoxyethoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methylcyclohexyl) - urea (trans), melting point 145—147°C (from methanol);
- from 4 - (β - <2 - β - methoxyethoxy - 5 - methoxy - benzamido> - ethyl) - benzenesulphonamide (melting point 177—178°C):—
- 60 (q) N - [4 - (β - <2 - β - methoxy - ethoxy - 5 - methoxy - benzamido> - ethyl) - benzene - sulphonyl] - N' - cyclohexyl - urea, melting point 140—142°C (from methanol) and

- (r) N - [4 - β - <2 - β - methoxy - ethoxy - 5 - methoxy - benzamido> - ethyl] - benzenesulphonyl] - N' - (4 - methylcyclohexyl) - urea (trans), melting point 163—165°C (from methanol);
In an analogous manner there are obtained
5 from 4 - (2 - methoxy - methoxy - benzamido - methyl) - benzenesulphonamide (melting point 176—178°C): — 5
- (s) N - [4 - (2 - methoxy - methoxy - benzamidomethyl) - benzenesulphonyl] - N' - cyclohexyl-urea, melting point 191—193°C,
10 from 4 - (β - <2 - methoxy - methoxy - benzamido> - ethyl) - benzenesulphonamide (melting point 169—170°C): — 10
- (t) N - [4 - (β - <2 - methoxy - methoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea, melting point 151—153°C (from methanol);
15 from 4 - (β - <4 - β - ethoxy - ethoxy - benzamido> - ethyl) - benzenesulphonamide (melting point 200—202°C): — 15
- (u) N - [4 - (β - <4 - β - ethoxy - ethoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methylcyclohexyl) - urea (trans), melting point 182—184°C (from methanol);
20 from 4 - (β - <2 - β - ethoxy - ethoxy - 5 - methyl - benzamido> - ethyl) - benzenesulphonamide (melting point 132—134°C): — 20
- (v) N - [4 - (β - <2 - β - ethoxy - ethoxy - 5 - methylbenzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea, melting point 121—123°C (from methanol) and 20
- (w) N - [4 - (β - <2 - β - ethoxy - ethoxy - 5 - methylbenzamido> - ethyl) - benzenesulphonyl] - N - (4 - methylcyclohexyl) - urea (trans), melting point 118—119°C (from methanol);
25 from 4 - (β - <2 - methoxy - methoxy - 5 - methyl - benzamido> - ethyl) - benzenesulphonamide (melting point 225—228°C): — 25
- (x) N - [4 - (β - <2 - methoxy - methoxy - 5 - methyl - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea, melting point 224—226°C (from methanol/dimethyl-formamide) and 30
- (y) N - [4 - (β - <2 - methoxy - methoxy - 5 - methyl - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 199—201°C (from methanol/dimethyl-formamide);
35 from 4 - (β - <2 - β - methoxy - ethoxy - 5 - fluoro - benzamido> - ethyl) - benzenesulphonamide (melting point 154—155°C): — 35
- (z) N - [4 - (β - <2 - β - methoxy - ethoxy - 5 - fluoro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea, melting point 132—134°C (from methanol), 40
- (aa) N - [4 - (β - <2 - β - methoxy - ethoxy - 5 - fluoro - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 161—163°C (from methanol) and 40
- (ab) N - [4 - (β - <2 - β - methoxy - ethoxy - 5 - fluoro - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - ethyl - cyclohexyl) - urea (trans), melting point 156—158°C (from methanol). 45

EXAMPLE 3.

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

- 8.7 Grams of N - [4 - (β - <2 - β - methoxy - ethoxy - benzamido> - ethyl) - benzene - sulphonyl] - methyl - urethane (melting point 123—125°C) are suspended
50 in 90 millilitres of xylene and 2 grams of cyclohexylamine are added at 80°C. The suspension is heated to 140—150°C and the methanol formed in the course of the reaction is distilled off. After about 30 minutes the suspension is allowed to cool, the reaction product is filtered off with suction and washed with methanol and ether.
55 The crude N - [4 - (β - <2 - β - methoxy - ethoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea after recrystallization from methanol melts at 160—162°C. In an analogous manner there is obtained N - [4 - (β - <2 - β - methoxy - ethoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans) of a melting point of 153—155°C (from methanol).

EXAMPLE 4.

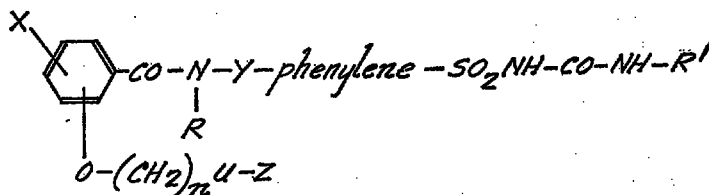
N-[4-(β -<2-methoxy-ethoxy-benzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea.

- 13 Grams of N - [4 - (β - <2 - methoxy - ethoxy - benzamido> - ethyl) - benzenesulphonyl] - urea (prepared by starting from the corresponding sulphonamide and reac-

tion with potassium cyanate, melting point 84°C) are successively diluted with 350 millilitres of toluene, 2.15 grams of glacial acetic acid and 3.7 grams of cyclohexylamine and then stirred for 3 hours at 120°C. After concentration under reduced pressure the residue is treated with ammonia of 1% strength, precipitated and crystallized from methanol. Melting point 160—162°C.

WHAT WE CLAIM IS:—

1. A compound of the formula



wherein

R represents a hydrogen atom or a lower alkyl or lower phenylalkyl radical,

R' represents:

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

(b) an alkoxyalkyl, alkylmercaptoalkyl or alkylsulphinylalkyl radical containing 4 to 8 carbon atoms of which at least two belong to the alkylene part of the alkoxyalkyl, alkylmercaptoalkyl or alkylsulphinylalkyl radical,

(c) a lower phenylalkyl or phenylcyclopropyl radical,

(d) a lower cyclohexyl-alkyl, cycloheptylmethyl, cycloheptylethyl or cyclo-octylmethyl radical,

(e) an endoalkylene-cyclohexyl, endoalkylene-cyclohexenyl, endoalkylene-cyclohexylmethyl or endoalkylene-cyclohexenylmethyl radical containing 1 or 2 endoalkylene-carbon atoms,

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

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

(h) a cyclohexenyl or cyclohexenylmethyl radical

(i) a heterocyclic ring containing 4 or 5 carbon atoms and one oxygen or sulphur atom as well as up to two ethylenic double bonds, or

(k) a heterocyclic ring containing 4 or 5 carbon atoms and one oxygen or sulphur atom, linked to the nitrogen atom by means of a methylene radical and in addition containing up to two ethylenic double bonds;

"phenylene" represents a phenylene group which may be unsubstituted or may be substituted by one or more substituents selected from halogen atoms and lower alkyl and lower alkoxy groups.

X represents a hydrogen or halogen atom or a lower alkyl, lower alkoxy, trifluoromethyl or nitro group,

Y represents a hydrocarbon chain containing 1 to 4 carbon atoms,

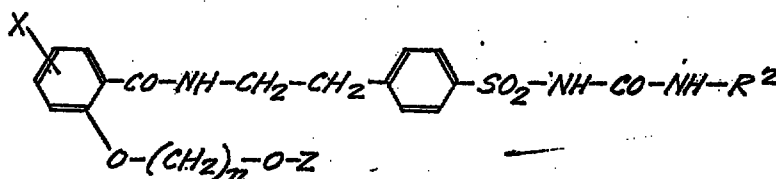
n represents 1, 2 or 3,

U represents oxygen or sulphur; and

Z represents a saturated or unsaturated, aliphatic or cyclo-aliphatic hydrocarbon radical containing up to 6 carbon atoms, a phenyl or a benzyl radical.

2. Compounds of the formula given in claim 1, wherein R, R', phenylene, X, Y, n, U and Z have the meanings given in claim 1 and the group $\text{O}-(\text{CH}_2)_n\text{U}-\text{Z}$ is in the 2-position and X is in the 4- or 5-position.

3. Compounds of the formula

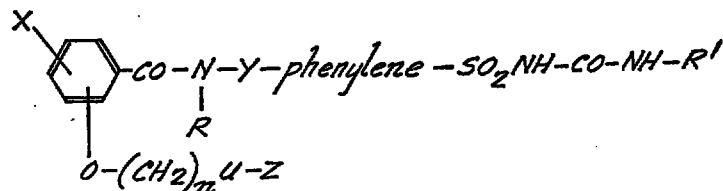


wherein X, n and Z have the meanings given above and R' is a cyclohexyl or lower alkyl-cyclohexyl radical.

tion with potassium cyanate, melting point 84°C) are successively diluted with 350 millilitres of toluene, 2.15 grams of glacial acetic acid and 3.7 grams of cyclohexylamine and then stirred for 3 hours at 120°C. After concentration under reduced pressure the residue is treated with ammonia of 1% strength, precipitated and crystallized from methanol. Melting point 160–162°C.

WHAT WE CLAIM IS:—

1. A compound of the formula



wherein

R represents a hydrogen atom or a lower alkyl or lower phenylalkyl radical,

R¹ represents:

- (a) an alkyl, alkenyl or mercaptoalkyl radical containing 2 to 8 carbon atoms,
- (b) an alkoxyalkyl, alkylmercaptoalkyl or alkylsulphinyllalkyl radical containing 4 to 8 carbon atoms of which at least two belong to the alkylene part of the alkoxyalkyl, alkylmercaptoalkyl or alkylsulphinyllalkyl radical,
- (c) a lower phenylalkyl or phenylcyclopropyl radical,
- (d) a lower cyclohexyl-alkyl, cycloheptylmethyl, cycloheptylethyl or cyclo-octylmethyl radical,
- (e) an endoalkylene-cyclohexyl, endoalkylene-cyclohexenyl, endoalkylene-cyclohexylmethyl or endoalkylene-cyclohexenylmethyl radical containing 1 or 2 endoalkylene-carbon atoms,
- (f) a lower alkylcyclohexyl or lower alkoxycyclohexyl radical,
- (g) a cycloalkyl radical containing 5 to 8 carbon atoms,
- (h) a cyclohexenyl or cyclohexenylmethyl radical
- (i) a heterocyclic ring containing 4 or 5 carbon atoms and one oxygen or sulphur atom at well as up to two ethylenic double bonds, or
- (k) a heterocyclic ring containing 4 or 5 carbon atoms and one oxygen or sulphur atom, linked to the nitrogen atom by means of a methylene radical and in addition containing up to two ethylenic double bonds;

"phenylene" represents a phenylene group which may be unsubstituted or may be substituted by one or more substituents selected from halogen atoms and lower alkyl and lower alkoxy groups.

X represents a hydrogen or halogen atom or a lower alkyl, lower alkoxy, trifluoromethyl or nitro group,

Y represents a hydrocarbon chain containing 1 to 4 carbon atoms,

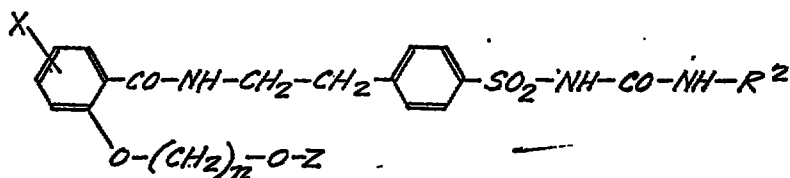
n represents 1, 2 or 3,

U represents oxygen or sulphur; and

Z represents a saturated or unsaturated, aliphatic or cyclo-aliphatic hydrocarbon radical containing up to 6 carbon atoms, a phenyl or a benzyl radical.

2. Compounds of the formula given in claim 1, wherein R, R¹, phenylene, X, Y, n, U and Z have the meanings given in claim 1 and the group —O—(CH₂)_n—U—Z is in the 2-position and X is in the 4- or 5-position.

3. Compounds of the formula

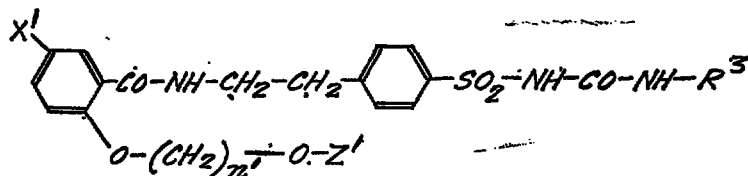


wherein X, n and Z have the meanings given above and R² is a cyclohexyl or lower alkyl-cyclohexyl radical.





4. Compounds of the formula



wherein

- 5 R^3 represents a cyclohexyl, 4-methyl-cyclohexyl or 4-ethyl cyclohexyl group,
5 X' represents a hydrogen, chlorine or fluorine atom, or a methyl or methoxy group,
 n' represents 1 or 2,
 Z' represents a methyl or ethyl group.
- 10 5. N - [4 - β - <2 - methoxy - ethoxy - benzamido> - ethyl) - benzenesulphonyl]-N'-cyclohexyl-urea. 10
6. N - [4 - (β - <2 - methoxy - methoxy - benzamido> - ethyl) - benzene-sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea.
- 15 7. N - [4 - (β - <2 - methoxy - methoxy - benzamido> - ethyl) - benzenesulphonyl]-N'-cyclohexyl-urea. 15
8. N - [4 - (β - <2 - β - methoxy - ethoxy - 5 - methyl - benzamido> - ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea. 15
9. N - [4 - (β - <2 - β - methoxy - ethoxy - 5 - chloro - benzamido> - ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea.
- 20 10. N - [4 - (β - <2 - β - methoxy - ethoxy - 5 - chloro - benzamido> - ethyl)-benzenesulphonyl]-N'-(4-methylcyclohexyl)-urea. 20
11. N - [4 - (β - <2 - β - methoxyethoxy - 5 - methoxy - benzamido> - ethyl)-benzenesulphonyl]-N'-(4-methyl-cyclohexyl)-urea.
12. N - [4 - (β - <2 - β - methoxy - ethoxy - benzamido> - ethyl) - benzene-sulphonyl]-N'-(4-methyl-cyclohexyl)-urea (trans).
- 25 13. N - [4 - (β - <2 - methoxy - methoxy - 5 - methyl - benzamido> - ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea. 25
14. N - [4 - (β - <2 - methoxy - methoxy - 5 - methyl - benzamido> - ethyl)-benzenesulphonyl]-N'-(4-methyl-cyclohexyl)-urea.
- 30 15. N - [4 - (β - <2 - β - methoxy - ethoxy - 5 - fluorbenzamido> - ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea. 30
16. N - [4 - (β - <2 - β - methoxy - ethoxy - 5 - fluorbenzamido> - ethyl)-benzenesulphonyl]-N'-(4-methyl-cyclohexyl)-urea (trans)
17. N - [4 - (β - <2 - β - methoxy - ethoxy - 5 - fluorbenzamido> - ethyl)-benzenesulphonyl]-N'-(4-ethyl-cyclohexyl)-urea (trans).
- 35 18. Any one of the compounds as claimed in claim 1 and which is described in any one of the Examples herein, other than the compounds claimed in claims 5 to 17. 35
19. Physiologically tolerable salts of any one of the compounds claimed in any one of claims 1 to 18.
- 40 20. A process for the manufacture of a compound as claimed in any one of claims 1 to 19, substantially as hereinbefore described. 40
21. 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 19 in admixture or conjunction with a pharmaceutically suitable carrier. 45
- 45 22. A preparation as claimed in claim 21, which contains in dosage unit form 0.5 to 100 milligrams of the active ingredient.
23. A preparation as claimed in claim 22, which contains in dosage unit form 2 to 10 milligrams of the active ingredient.

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