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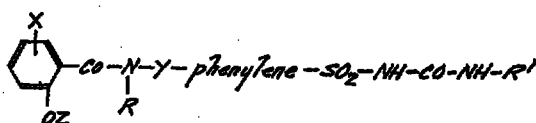
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COMPLETE SPECIFICATION

Benzenesulphonyl-Ureas and Process for their Manufacture

We: **FARBWERKE HOECHST AKTIENGESELLSCHAFT** Vornals 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 general formula



in which:—

R represents a hydrogen atom or a lower alkyl or a phenyl-lower alkyl radical,

R¹ represents

(a) an alkyl, alkenyl or mercapto-alkyl radical containing 2 to 8 carbon atoms,
(b) an alkoxy-alkyl, alkyl-mercaptoalkyl or alkylsulphinylalkyl radical containing 4 to 8 carbon atoms of which at least 2 belong to the alkylene part of the alkoxy-alkyl, alkyl-mercaptoalkyl or alkyl-sulphinyl-alkyl radical,

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

(d) a cyclohexyl-lower alkyl, cycloheptylmethyl, cycloheptyl-ethyl or cyclooctyl-methyl radical,

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

(f) a lower alkyl-cyclohexyl 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 1 oxygen or 1 sulphur atom and optionally 1 or 2 ethylenic double bonds, or

(k) a heterocyclic ring containing 4 or 5 carbon atoms and 1 oxygen or 1 sulphur atom and optionally 1 or 2 ethylenic double bonds, said heterocyclic ring being linked to the nitrogen atom by means of a methylene group,

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

Z represents a saturated or unsaturated, aliphatic hydrocarbon radical containing 5 or 6 carbon atoms, or a phenyl group which may be substituted by a lower alkyl radical, or by a lower alkoxy radical, or by a CF₃ group or by 1 chlorine, bromine, or fluorine atom,

X represents a halogen atom or a lower alkyl or lower alkoxy radical, or a —CF₃ or

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—NO₂ group, or may also represent a hydrogen atom when Z represents a phenyl group or a phenyl group which is substituted in the aforementioned manner, the substituent X preferably standing in the 4- or in the 5-position to the carbonamide group,

5 and in which the phenylene group may be unsubstituted or substituted by one or more substituents selected from halogen atoms, lower alkyl groups, and lower alkoxy groups.

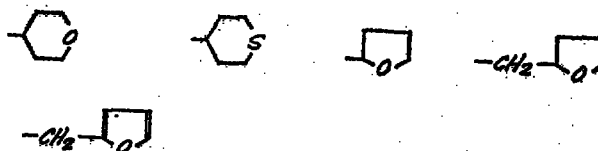
10 The terms "lower alkyl" and "lower alkoxy" are used throughout the specification to mean an alkyl or alkoxy radical containing 1 to 4 carbon atoms in a straight or branched chain.

In accordance with the definitions given above, R may represent, for example, a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, benzyl, α - or β -phenyl-ethyl, α -, β - or γ -phenyl-propyl radical. Compounds in which R represents a methyl or benzyl radical and especially those in which R represents a hydrogen atom are preferred.

15 R¹ may represent, for example, an ethyl, propyl, isopropyl, butyl, isobutyl, secondary butyl, straight chain or branched amyl (pentyl), hexyl, heptyl or octyl radical; furthermore, it may represent radicals which correspond to the aforementioned hydrocarbon radicals and which contain an ethylenic double bond, for example, an allyl or crotyl radical; furthermore alkyl radicals containing 2 to 8 carbon atoms and 1 mercapto group, for example, β -mercapto-ethyl, or higher mercapto-alkyl radicals. Furthermore, R¹ may represent a γ -methoxypropyl, δ -methoxy-*n*-butyl, β -ethoxyethyl, γ -ethoxy-propyl, δ -ethoxybutyl or a higher alkoxy-ethyl, -propyl or -butyl radical or a corresponding group that contains instead of the oxygen atom a sulphur atom or —SO— group. Furthermore, R¹ may represent: a benzyl, α -phenyl-ethyl, β -phenyl-ethyl, α -, β - or γ -phenyl-propyl or a phenyl-butyl radical.

20 There are preferred, more especially, compounds containing as R¹ a cycloaliphatic hydrocarbon radical which in the case of cyclohexyl, may be substituted by one or more substituents selected from alkyl and alkoxy radicals, or which may be linked to the nitrogen atom by means of an alkylene group. As examples of such radicals, there may be mentioned cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, methyl-cyclohexyl, ethyl-cyclohexyl, propyl-cyclohexyl and isopropyl-cyclohexyl, methoxy-cyclohexyl, ethoxy-cyclohexyl, propoxy-cyclohexyl and isopropoxy-cyclohexyl; the alkyl or alkoxy radicals may be present in the 2-, 3- or, preferably, in the 4-position, and in the cis- as well as in the trans- position. Furthermore, there may be mentioned cyclohexylmethyl, α - or β -cyclohexyl-ethyl, cyclohexylpropyls, endomethylene-cyclohexyl (2,2,1-bicycloheptyl), endoethylene-cyclohexyl (2,2,2-bi-cyclo-octyl), endomethylene-cyclohexenyl, endoethylene-cyclohexenyl, endomethylene-cyclohexylmethyl, endoethylene-cyclohexylmethyl, endomethylenecyclohexenylmethyl or endoethylene-cyclohexenylmethyl, and α - or β -phenyl-cyclopropyl, in the cis- or in the trans- form. Finally, R² may represent heterocyclic rings which contains, in addition to 4 or 5 carbon atoms, 1 oxygen or 1 sulphur atom and optionally 1 or 2 double bonds and which may be bound to the adjacent nitrogen atom by a methylene group.

45 Examples of such heterocyclic rings are:



Examples of the bridge member Y are:

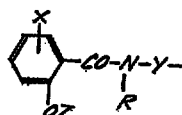
50 —CH₂—, —CH₂—CH₂—, —CH(CH₃)—, —CH₂—CH₂—CH₂—, —CH(CH₃)—CH₂—, —CH₂—CH(CH₃)—, —C(CH₃)₂—, —CH₂—CH₂—CH₂—CH₂—, —CH(CH₃)—CH₂—CH₂—, —CH₂—CH(CH₃)—CH₂—, —CH₂—CH₂—CH(CH₃)—, —CH(CH₃)—CH(CH₃)—, —C(CH₃)₂—CH₂—, —CH₂—C(CH₃)₂—, —CH(C₂H₅)—, —C(CH₃)(C₂H₅)—, wherein —CH₂—CH₂—, —CH(CH₃)—CH₂— and —CH₂—CH(CH₃)— are preferred.

55 The phenylene radical indicated in the formula by -phenylene- is preferably unsubstituted, but may also be substituted by one or more substituents selected from halogen atoms, lower alkyl radicals or lower alkoxy radicals. It may contain the re-

maining parts of the molecule in *o*-, *m*- or *p*-position to one another, the *p*-position being preferred.

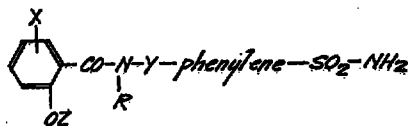
The present invention furthermore provides a process for the manufacture of the above-identified benzenesulphonyl ureas. Thus, the benzenesulphonyl-ureas of the present invention may be prepared by

(a) reacting a benzenesulphonyl-isocyanate, benzene-sulphonyl-carbamic acid ester, benzenesulphonyl-thiolcarbamic acid ester, benzenesulphonyl-urea, benzenesulphonyl-semicarbazide or benzenesulphonyl-semicarbazone carrying the substituent



with an R^1 -substituted amine or a salt thereof:

(b) reacting a benzene-sulphonamide of the formula



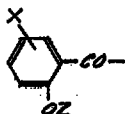
or a salt thereof with an R^1 -substituted isocyanate, carbamic acid ester, thiolcarbamic acid ester, carbamic acid halide or urea,

(c) hydrolysing a correspondingly substituted benzene-sulphonyl-isourea ether, benzenesulphonyl-isourea ester, benzenesulphonyl-isothiurea ether, benzenesulphonyl-parabanic acid or benzenesulphonyl-haloformic acid amidine,

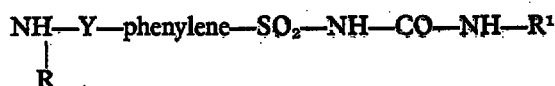
(d) effecting a chemical addition of water to a correspondingly substituted benzenesulphonyl carbodiimide,

(e) in a correspondingly substituted benzenesulphonylthiourea, replacing the sulphur atom by an oxygen atom,

(f) introducing by acylation the radical

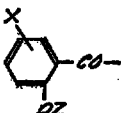


in one or several steps into a benzenesulphonyl-urea of the formula



and, if desired, converting the reaction product into a salt by treatment with an alkaline agent.

Depending on the nature of the group



one or more of the aforesaid processes may in certain cases be unsuitable for the preparation of some individual compounds covered by the general formula. These particular cases are relatively unusual and are easily recognized by the expert, so that it is not difficult to select another successful method of synthesis from those described above.

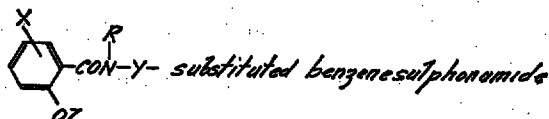
Instead of the benzenesulphonyl-isocyanates, there may also be used a reaction product of the benzenesulphonylisocyanate with an acid amide such, for example, as caprolactam or butyrolactam, furthermore with a weakly basic amine such, for example, as carbazole.

The above-mentioned benzenesulphonyl-carbamic acid esters or benzenesulphonyl-thiolcarbamic acid esters may contain in the alcohol component an alkyl group or an aryl group or even a heterocyclic group. Since this group is separated during the reaction, its chemical constitution has no influence on the character of the final products and may, therefore, be varied within wide limits. The same applies to the R¹-substituted carbamic acid esters or to the corresponding thiolcarbamic acid esters.

As carbamic acid halides, the chlorides are advantageously used.

The benzenesulphonyl-ureas used as starting substances in the process of the present invention may be unsubstituted at the side of the urea molecule opposite to the sulphonyl group or may be mono-substituted or, particularly, di-substituted. Since these substituents are separated during the reaction with amines, their character may be varied within wide limits. In addition to benzenesulphonyl-ureas which are substituted by alkyl, aryl, acyl or heterocyclic groups, there may also be used bis-(benzenesulphonyl)-ureas or bis-(benzenesulphonyl)-ureas which carry a further substituent, for example, a methyl group, at one of the nitrogen atoms. For example, such bis-(benzenesulphonyl)-ureas or also N-benzenesulphonyl-N'-acyl ureas may be treated with cyclohexylamine or with *p*-methyl-cyclohexylamine and the salts obtained may be heated to elevated temperatures, in particular to temperatures above 100°C., when they undergo an elimination reaction to form the corresponding benzenesulphonyl urea of the invention.

Furthermore, it is possible to start from a urea of the formula R¹-NH-CO-NH₂ which may carry one or, especially, two substituents at the free nitrogen atom and to react this with a



As such starting substances, there may be used, for example, N-cyclohexyl-urea or N-(4-methyl-cyclohexyl)-urea, the corresponding N'-acetyl-, N'-nitro-, N'-cyclohexyl-, N'-(4-methyl-cyclohexyl)-, N',N'-diphenyl- (wherein both phenyl radicals may also be substituted or linked with one another either directly or through a bridge member such, for example, as -CH₂-, -NH-, -O- or -S-), N'-methyl-N'-phenyl-, N',N'-dicyclohexyl-ureas, and R'-substituted-carbamoyl-imidazoles or -triazoles.

The hydrolysis of the benzenesulphonyl-parabanic acids, benzenesulphonyl-iso-urea ethers, benzenesulphonyl-isothioureas, benzenesulphonyl-isourea esters or benzenesulphonyl-haloformic acid amidines mentioned as starting substances is suitably carried out in an alkaline medium. Isourea ethers and isourea esters may also be hydrolysed successfully in an acid medium.

In the correspondingly substituted benzenesulphonylthioureas the sulphur atom can be replaced by an oxygen atom, for example with the aid of an oxide or salt of a heavy metal or also by the use of an oxidizing agent such, for example, as hydrogen peroxide, sodium peroxide or nitrous acid.

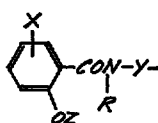
The thioureas can also be desulphurized by treatment with phosgene or phosphorus pentachloride. Chloroformic acid amidines or chloroformic acid carbodiimides obtained as intermediate products can be converted into benzenesulphonyl-ureas by an appropriate treatment, for example by hydrolysis or the addition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

The isothioureas behave in an analogous manner to the thioureas and in the process of the invention are equivalent as starting substances for the desulphurizing reactions.

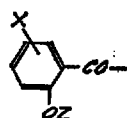
The acylation of aminoethyl-benzenesulphonyl-ureas may be carried out either in one step, for example by reaction of a correspondingly substituted benzoic acid halide, or it may be carried out in several steps. One example of the numerous possibilities of stepwise acylation is the reaction of a corresponding aminoethyl-benzene-sulphonyl-urea with a 2-alkoxy- or 2-aryloxy-benzoyl chloride and subsequent introduction of a halogen atom into the benzene nucleus of the benzamido group. Another example is the introduction of a correspondingly substituted thio-benzoyl group, and the conversion of the reaction product into the corresponding benzamide derivative.

With regard to the reaction conditions, the manner of carrying out the process of the present invention may, in general, vary within wide limits and can be adapted to each individual case. For example, the reactions may be carried out with the use of solvents, at room temperature or at an elevated temperature.

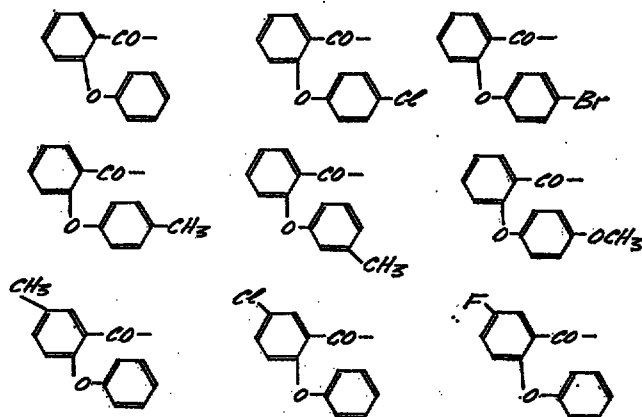
As starting substances, there may be used compounds containing a benzene radical substituted by the group

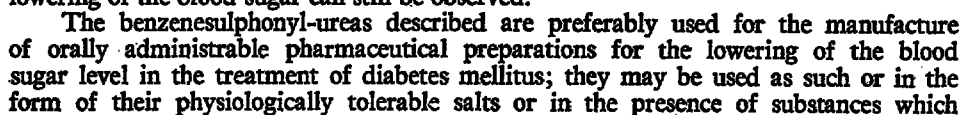


As the part



of this formula there may be mentioned





cause such salt formation. For the formation of salts, there may be used, for example, alkaline agents such, for example, as alkali metal hydroxides or alkaline earth metal hydroxides, alkali metal carbonates or bicarbonates or alkaline earth metal carbonates or bicarbonates.

The invention, therefore, also provides pharmaceutical preparations of the above kind which comprise a benzenesulphonylurea of the present invention or a physiologically tolerable salt thereof in admixture or conjunction with a pharmaceutically suitable carrier.

The pharmaceutical preparations are advantageously in the form of tablets containing, in addition to the products of the present invention, the usual pharmaceutically suitable carriers such, for example, as talc, starch, lactose, tragacanth or magnesium stearate.

A pharmaceutical preparation containing one of the aforesaid benzenesulphonylureas as the active substance, for example, a tablet or a powder, with or without the aforesaid carriers, is advantageously brought into a suitable unit dosage form. The dose chosen should comply with the activity of the benzenesulphonyl-urea used and the desired effect. Advantageously, the dosage per unit amounts to about 0.5 to 100 mg, preferably 2 to 10 mg, but considerably higher or lower dosage units may also be used which, if desired, are divided or multiplied prior to their administration.

The following Examples illustrate the invention:

EXAMPLE 1

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

9.9 grams of 4-(β -<2-phenoxy-benzamido>-ethyl)-benzenesulphonamide (melting point 187—188°C, prepared from 2-phenoxy-benzoic acid chloride and 4-(β -aminoethyl)-benzenesulphonamide) are suspended in a mixture of 12.5 ml of a 2N sodium hydroxide solution and 50 ml of acetone; 3.3 grams of cyclohexyl-isocyanate are added dropwise, at 0—5°C to this suspension. The whole is stirred for 3 hours at room temperature, the reaction mixture is diluted with water, undissolved matter is filtered off and the filtrate is acidified with dilute hydrochloric acid. The N-[4-(β -<2-phenoxy-benzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea, which separates in crystalline form, melts after recrystallisation from methanol at 168—170°C.

In analogous manner, there are obtained

(a) N-[4-(β -<2-phenoxy-benzamido>-ethyl)-benzenesulphonyl]-N'-(4-methylcyclohexyl)-urea (trans), melting point 186—188°C (from methanol) and

(b) N-[4-(β -<2-phenoxy-benzamido>-ethyl)-benzenesulphonyl]-N'-butyl urea, melting point 138—140°C (from methanol);

from 4-(β -<2-isoamyloxy-5-methyl-benzamido>-ethyl)-benzenesulphonamide (melting point 152—153°C):—

(c) N-[4-(β -<2-isoamyloxy-5-methyl-benzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea, melting point 163—164°C (from methanol) and

(d) N-[4-(β -<2-isoamyloxy-5-methyl-benzamido>-ethyl)-benzenesulphonyl]-N'-(4-methyl-cyclohexyl)-urea (trans), melting point 156—158°C (from methanol);

from 4-(β -<2-isoamyloxy-5-chloro-benzamido>-ethyl)-benzenesulphonamide (melting point 147—148°C):—

(e) N-[4-(β -<2-isoamyloxy-5-chloro-benzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea, melting point 173—174°C (from methanol) and

(f) N-[4-(β -<2-isoamyloxy-5-chloro-benzamido>-ethyl)-benzenesulphonyl]-N'-(4-methyl-cyclohexyl)-urea (trans), melting point 165—166°C (from methanol);

from 4-(β -<2-(4-methyl-phenoxy)-benzamido>-ethyl)-benzenesulphonamide (melting point 176—177°C):—

(g) N-[4-(β -<2-(4-methyl-phenoxy)-benzamido>-ethyl)-benzenesulphonyl]-N'-(4-methyl-cyclohexyl)-urea (trans), melting point 174—176°C (from methanol);

from 4-(β -<2-phenoxy-4-chloro-benzamido>-ethyl)-benzenesulphonamide (melting point 191—192°C):—

(h) N-[4-(β -<2-phenoxy-4-chloro-benzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea, melting point 168—169°C (from methanol) and

- (i) N - [4 - (β - <2 - phenoxy - 4 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 155—156°C (from methanol);
- 5 from 4 - (β - <2 - (4 - methyl - phenoxy) - 4 - chloro - benzamido> - ethyl) - benzenesulphonamide (melting point 189—190°C):— 5
- (j) N - [4 - (β - <2 - (4 - methyl - phenoxy) - 4 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea, melting point 114—116°C (decomposition) (from methanol),
- 10 (k) N - [4 - (β - <2 - (4 - methylphenoxy) - 4 - chlorobenzamido> - ethyl) - benzenesulphonyl] - N' - butyl - urea, melting point 134—136°C (from methanol) and 10
- (l) N - [4 - (β - <2 - (4 - methyl - phenoxy) - 4 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 166—168°C (from methanol);
- 15 from 4 - (β - <2 - phenoxy - 5 - chloro - benzamido> - ethyl) - benzene - sulphonamide (melting point 156—158°C):— 15
- (m) N - [4 - (β - <2 - phenoxy - 5 - chloro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea, melting point 175—177°C (from a mixture of methanol and dimethylformamide) and
- 20 (n) N - [4 - (β - <2 - phenoxy - 5 - chloro - benzamido> - ethyl) - benzene - sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 143—145°C (from methanol);
- 25 from 4 - (β - <2 - phenoxy - 5 - nitro - benzamido> - ethyl) - benzene - sulphonamide (melting point 159—160°C):— 25
- (o) N - [4 - (β - <2 - phenoxy - 5 - nitro - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea, melting point 134—136°C (from methanol) and
- (p) N - [4 - (β - <2 - phenoxy - 5 - nitro - benzamido> - ethyl) - benzene - sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 167—169°C (from methanol); and
- 30 from 4 - (β - <2 - n - amyloxy - 5 - chloro - benzamido> - ethyl) - benzene - sulphonamide (melting point 143—144°C):— 30
- (q) N - [4 - (β - <2 - n - amyloxy - 5 - chloro - benzamido> - ethyl) - benzene - sulphonyl] - N' - cyclohexyl - urea, melting point 169—170°C (from a mixture of methanol and dimethylformamide) and
- 35 (r) N - [4 - (β - <2 - n - amyloxy - 5 - chloro - benzamido> - ethyl) - benzene - sulphonyl] - N' - (4 - methyl - cyclohexyl) - urea (trans), melting point 168—170°C (from a mixture of methanol and dimethylformamide). 35

EXAMPLE 2

- N-[4-(β-<2-phenoxy-5-methyl-benzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea 40
- 9.4 grams of N - [4 - (β - <2 - phenoxy - 5 - methyl - benzamido> - ethyl) - benzenesulphonyl] - methyl - urethane (melting point 165—167°C) are suspended in 150 ml of xylene; 2 grams of cyclohexylamine are added at 80°C to this suspension. The whole is then heated to 140°C, while stirring vigorously, and kept for one hour at this temperature, during which time the methanol formed separates by distillation. After cooling, the solvent is decanted and the oily residue is triturated with methanol. The crystals thus obtained, constituting N - [4 - (β - <2 - phenoxy - 5 - methyl - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea, are recrystallized from methanol and melt at 129—131°C. 45

- In analogous manner there is obtained 50
- N - [4 - <2 - phenoxy - 5 - methyl - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - ethyl - cyclohexyl - urea (trans), melting point 153—154°C (from methanol). 50

EXAMPLE 3

- N-[4-(β-<2-phenoxy-benzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea 55
- 7.4 grams of N,N-diphenyl-N'-cyclohexyl-urea and 10.5 grams of the sodium salt of 4-(β-<2-phenoxy-benzamido>-ethyl)-benzenesulphonamide are heated for 7 hours in an oil bath to 100°C, in 25 ml of dimethylformamide. When the solution has cooled, it is diluted with water, sodium hydroxide solution is added and the diphenyl-amine that has formed is extracted with ether. The aqueous solution is filtered and acidified with dilute hydrochloric acid. The reaction product is separated by filtration with suction and recrystallized from methanol. N - [4 - (β - <2 - phenoxy- 60

benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea melts at 168—170°C.

EXAMPLE 4

N-[4-(β-⟨2-phenoxy-benzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea

5 a) 2 grams of N - [4 - (β - ⟨2 - phenoxy - benzamido> - ethyl) - benzene -
sulphonyl] - N' - cyclohexyl - thiourea (melting point 148—150°C, from a mixture
10 of methanol and dioxane, prepared from 4 - (β - ⟨2 - phenoxy - benzamido> - ethyl) -
benzenesulphonamide and cyclohexylisothiocyanate by boiling in acetone in the pre-
15 sence of potassium carbonate), are dissolved in a mixture of 40 ml of dioxane and 40
ml of a 2N sodium hydroxide solution. 1 gram of mercuric oxide is added and the
whole is stirred for 4 hours at about 60°C. When the reaction mixture has cooled, the
mercury sulphide that has formed is removed by filtration with suction, the filtrate is
diluted with water and acidified. A crystalline precipitate constituting N - [4 - (β -
⟨2 - phenoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea is
obtained which is filtered off with suction, washed with water and recrystallized from
methanol. The substance melts at 168—170°C.

20 b) 2 grams of N - [4 - (β - ⟨2 - phenoxy - benzamido> - ethyl) - benzene -
sulphonyl] - N' - cyclohexyl - thiourea are added, while stirring, to 40 ml of a 2N
sodium hydroxide solution. The suspension thus obtained of the sodium salt of the
sulphonylthiourea that has formed is combined with 10 ml of hydrogen peroxide
25 having a concentration of 35% by weight and the whole is heated for 30 minutes on
the steam bath. The reaction mixture is cooled, acidified with dilute hydrochloric acid
and the precipitate constituting N - [4 - (β - ⟨2 - phenoxy - benzamido> - ethyl) -
benzenesulphonyl] - N' - cyclohexyl - urea is filtered off with suction. After washing
with water the substance is recrystallized from methanol. Melting point 168—
170°C.

EXAMPLE 5

N-[4-(β-⟨2-phenoxy-benzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea

30 a) 5.4 grams of N - [4 - (β - ⟨2 - phenoxy - benzamido> - ethyl) - benzene -
sulphonyl] - N' - cyclohexyl - thiourea are dissolved in 250 ml of methanol. 2.16
g of mercuric oxide and a pinch of potassium carbonate are added and the whole is
heated, while stirring and under reflux, to the boiling temperature. After 4 hours
35 the mercury sulphide that has formed is separated by filtration with suction and the
filtrate is concentrated.

The residue obtained constituting N - [4 - (β - ⟨2 - phenoxy - benzamido> -
ethyl) - benzenesulphonyl] - N' - cyclohexyl - isourea methyl ether crystallizes upon
standing overnight. After recrystallization from dilute methanol the substance melts
at 92—94°C.

40 b) 1 gram of the N - [4 - (β - ⟨2 - phenoxy - benzamido> - ethyl) - benzene -
sulphonyl] - N' - cyclohexyl - isourea methyl ether obtained according to a) are
dissolved in a mixture of 20 ml of dioxane and 30 ml of a 2N sodium hydroxide
solution. The whole is heated for 4 hours, while stirring and under reflux, to 90°C,
45 poured into water and acidified. The precipitate obtained constituting N - [4 - (β -
⟨2 - phenoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea
melts at 168—170°C after recrystallization from methanol.

EXAMPLE 6

N-[4-(β-⟨2-phenoxy-benzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea

50 a) 9.9 grams of 4 - (β - ⟨2 - phenoxy - benzamido> - ethyl) - benzenesulphon-
amide are suspended in 30 ml. of ethanol having a concentration of 98% by volume.
A solution of 2.43 grams of potassium cyanate in 5 ml of water is added and the
whole is heated, for 2½ hours and under reflux, to the boiling temperature. After about
55 30 minutes a clear solution is obtained from which crystals separate. After standing
overnight, the crystal magma is combined with a large quantity of ammonia having
a concentration of 1% by weight, whereupon the magma is almost completely dis-
solved. The solution is filtered with animal charcoal and acidified. The precipitate
obtained, constituting N - [4 - (β - ⟨2 - phenoxy - benzamido> - ethyl) - benzene-
sulphonyl] - urea is filtered off with suction and recrystallized from dilute meth-
60 anol. The dried substance melts at 155—157°C.

b) 4.39 grams of the N - [4 - (β - <2 - phenoxy - benzamido> - ethyl) - benzenesulphonyl] - urea obtained according to a) are suspended in 40 ml of dioxane, to this suspension 40 ml of dimethylformamide and 1 gram of cyclohexylamine are added. The whole is heated for about 4 hours and under reflux to the boiling temperature, poured into a large quantity of ammonia having a concentration of 1% by weight and the solution thus obtained is acidified with hydrochloric acid.

The precipitate constituting crude N - [4 - (β - <2 - phenoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea is filtered off with suction and recrystallized from methanol. Melting point 168—170°C.

EXAMPLE 7

N-[4-(γ-<2-phenoxy-5-nitrobenzamido>-propyl)-benzenesulphonyl]-N'-cyclohexyl-urea

16 grams of N - [4 - (γ - acetamido - propyl) - benzenesulphonyl] - N' - cyclohexyl - urea are heated for 3 hours to 120°C with 100 ml of NaOH having a strength of 10%. After cooling the resulting mixture is acidified, filtered and the clear filtrate is neutralized by the addition of sodium bicarbonate. The N - [4 - (γ - amino - propyl) - benzenesulphonyl] - N' - cyclohexyl - urea that has precipitated is recrystallized from aqueous methanol and melts at 188°C.

10 grams of this sulphonyl-urea are stirred for 12 hours, at 35—40°C, with 6.6 grams of 2-chloro-5-nitrobenzoylchloride and 5 grams of pyridine in 80 ml of chloroform. After removal of the chloroform under reduced pressure, the residue is dissolved in an aqueous soda solution having a strength of 1%, the solution is shaken with ether and acidified with hydrochloric acid. The N - [4 - (γ - <2 - chloro - 5 - nitro - benzamido> - propyl) - benzenesulphonyl] - N' - cyclohexyl - urea obtained is recrystallized from methanol and melts at 176°C.

5 grams of this sulphonyl-urea are dissolved in 70 ml of glycol monomethyl ether and this solution is combined with 3.7 grams of phenyl sodium; the whole is then heated for 30 minutes to 125°C. After cooling, the solution is poured into ice-water acidified by a small amount of hydrochloric acid, the precipitate that has separated is extracted with ammonia having a strength of 1%, acidified again and recrystallized from ethanol. N - [4 - (γ - <2 - phenoxy - 5 - nitro - benzamido> - propyl) - benzenesulphonyl] - N' - cyclohexyl - urea melts at 90—92°C.

EXAMPLE 8

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

6 grams of N - [4 - (β - <2 - phenoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - (2,5 - endomethylene - cyclohexyl - methyl) - thiourea (melting point 183—185°C, from dilute methanol, prepared by boiling for several hours 4 - (β - <2 - phenoxy - benzamido> - ethyl) - benzenesulphonamide with 2,5 - endomethylene - cyclohexyl - methyl isothiocyanate in dioxane in the presence of potassium carbonate) are suspended in 100 ml of a 2N sodium hydroxide solution. 10 ml of hydrogen peroxide having a concentration of 35% by weight are added and the whole is heated for 30 minutes on the steam bath. After cooling, the reaction solution is acidified, the crystal magma is filtered off with suction, washed with water and taken up in ethyl acetate. After separation of the aqueous layer, diisopropyl ether is added. The smeary product that has precipitated is separated by decanting the mixture of ethyl acetate and diisopropyl ether; it is then recrystallized from methanol. The N - [4 - (β - <2 - phenoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - (2,5 - endomethylene - cyclohexyl - methyl) - urea thus obtained melts at 138—140°C.

EXAMPLE 9

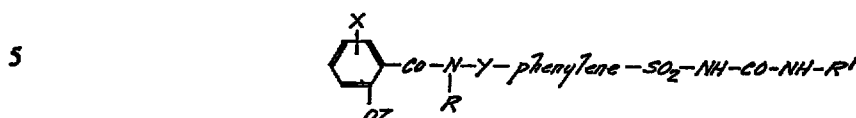
N-[4-(β-<2-phenoxy-benzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea

5.4 grams of N - [4 - (β - <2 - phenoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - thiourea are dissolved in 60 ml of methanol. An excess quantity of methyl iodide is added and the whole is heated, for 45 minutes under reflux, to the boiling temperature and subsequently concentrated under reduced pressure. The residue constituting N - [4 - (β - <2 - phenoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - isothiurea methyl ether is dissolved in methanol. 0.54 gram of sodium methylate are added and the whole is heated for 2 hours under reflux to the boiling temperature, poured into water and acidified with acetic acid. A crystalline precipitate constituting N - [4 - (β - <2 - phenoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexylurea is obtained which is filtered off

with suction and dried. The substance melts at 168—170°C, after recrystallization from methanol.

WHAT WE CLAIM IS:—

1. Benzenesulphonyl-ureas of the formula



in which:—

R represents a hydrogen atom or a lower alkyl or a phenyl-lower alkyl radical,

R¹ represents

- (a) an alkyl, alkenyl or mercapto-alkyl radical containing 2 to 8 carbon atoms,
- (b) an alkoxy-alkyl, alkyl-mercaptoalkyl or alkyl-sulphinylalkyl radical containing 4 to 8 carbon atoms of which at least 2 belong to the alkylene part of the alkoxy-alkyl, alkyl mercaptoalkyl or alkyl-sulphinylalkyl radical,
- (c) a phenyl-lower alkyl or phenyl-cyclo-propyl radical,
- (d) a cyclohexyl-lower alkyl, cycloheptyl-methyl, cycloheptyl-ethyl or cyclooctyl-methyl radical,
- (e) an endoalkylene-cyclohexyl, endoalkylene-cyclohexenyl, endoalkylene-cyclohexylmethyl or endoalkylene-cyclohexenylmethyl radical containing 1 or 2 carbon atoms in the endoalkylene part,
- (f) a lower alkyl-cyclohexyl 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 1 oxygen or 1 sulphur atom and optionally 1 or 2 ethylenic double bonds, or
- (k) a heterocyclic ring containing 4 or 5 carbon atoms and 1 oxygen or 1 sulphur atom and optionally 1 or 2 ethylenic double bonds, said heterocyclic ring being linked to the nitrogen atom by means of a methylene group,

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

Z represents a saturated or unsaturated, aliphatic hydrocarbon radical containing 5 or 6 carbon atoms, or a phenyl group which may be substituted by a lower alkyl radical, or by a lower alkoxy radical, or by a CF₃ group or by 1 chlorine, bromine, or fluorine atom,

X represents a halogen atom or a lower alkyl or a lower alkoxy radical or a —CF₃ or —NO₂ group, or may also represent a hydrogen atom when Z represents a phenyl group or a phenyl group which is substituted in the aforementioned manner, the group X preferably standing in the 4- or in the 5-position to the carbonamide group,

and in which the phenylene group may be unsubstituted or substituted by one or more substituents selected from halogen atoms, lower alkyl groups, and lower alkoxy groups.

2. Benzenesulphonyl-ureas as claimed in claim 1, wherein R represents a hydrogen atom.

3. Benzenesulphonyl-ureas as claimed in claim 1 or claim 2, wherein X represents a chlorine atom in the 5-position to the carbonamide group.

4. Benzenesulphonyl-ureas as claimed in claim 1 or claim 2, wherein X represents a methyl group in the 5-position to the carbonamide group.

5. Benzenesulphonyl-ureas as claimed in any one of claims 1 to 4, wherein R¹ represents a cyclohexyl radical.

6. Benzenesulphonyl-ureas as claimed in any one of claims 1 to 4, wherein R¹ represents a 4-methyl-cyclohexyl group.

7. Benzenesulphonyl-ureas as claimed in any one of claims 1 to 6, wherein "phenylene" is an unsubstituted paraphenylene group.

8. Benzenesulphonyl-ureas as claimed in any one of claims 1 to 7, wherein Y represents a dimethylene group.

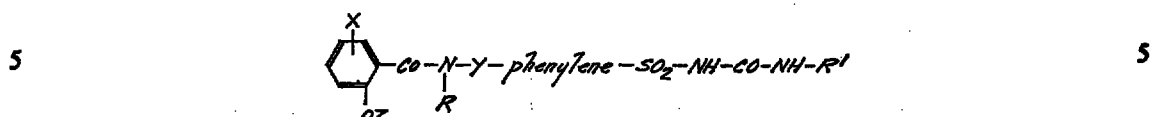
9. N - [4 - (β - <2 - isoamyloxy - 5 - methyl - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea.

10. N - [4 - (β - <2 - phenoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea.

with suction and dried. The substance melts at 168—170°C, after recrystallization from methanol.

WHAT WE CLAIM IS:—

1. Benzenesulphonyl-ureas of the formula



in which:—

R represents a hydrogen atom or a lower alkyl or a phenyl-lower alkyl radical,

R¹ represents

- (a) an alkyl, alkenyl or mercapto-alkyl radical containing 2 to 8 carbon atoms,
- (b) an alkoxy-alkyl, alkyl-mercaptoalkyl or alkyl-sulphinylalkyl radical containing 4 to 8 carbon atoms of which at least 2 belong to the alkylene part of the alkoxy-alkyl, alkyl mercaptoalkyl or alkyl-sulphinylalkyl radical,
- (c) a phenyl-lower alkyl or phenyl-cyclo-propyl radical,
- (d) a cyclohexyl-lower alkyl, cycloheptyl-methyl, cycloheptyl-ethyl or cyclooctyl-methyl radical,
- (e) an endoalkylene-cyclohexyl, endoalkylene-cyclohexenyl, endoalkylene-cyclohexylmethyl or endoalkylene-cyclohexenylmethyl radical containing 1 or 2 carbon atoms in the endoalkylene part,
- (f) a lower alkyl-cyclohexyl 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 1 oxygen or 1 sulphur atom and optionally 1 or 2 ethylenic double bonds, or
- (k) a heterocyclic ring containing 4 or 5 carbon atoms and 1 oxygen or 1 sulphur atom and optionally 1 or 2 ethylenic double bonds, said heterocyclic ring being linked to the nitrogen atom by means of a methylene group,

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

Z represents a saturated or unsaturated, aliphatic hydrocarbon radical containing 5 or 6 carbon atoms, or a phenyl group which may be substituted by a lower alkyl radical, or by a lower alkoxy radical, or by a CF₃ group or by 1 chlorine, bromine, or fluorine atom,

X represents a halogen atom or a lower alkyl or a lower alkoxy radical or a —CF₃ or —NO₂ group, or may also represent a hydrogen atom when Z represents a phenyl group or a phenyl group which is substituted in the aforementioned manner, the group X preferably standing in the 4- or in the 5-position to the carbonamide group,

and in which the phenylene group may be unsubstituted or substituted by one or more substituents selected from halogen atoms, lower alkyl groups, and lower alkoxy groups.

2. Benzenesulphonyl-ureas as claimed in claim 1, wherein R represents a hydro- gen atom.

3. Benzenesulphonyl-ureas as claimed in claim 1 or claim 2, wherein X rep- resents a chlorine atom in the 5-position to the carbonamide group.

4. Benzenesulphonyl-ureas as claimed in claim 1 or claim 2, wherein X repre- sents a methyl group in the 5-position to the carbonamide group.

5. Benzenesulphonyl-ureas as claimed in any one of claims 1 to 4, wherein R¹ represents a cyclohexyl radical.

6. Benzenesulphonyl-ureas as claimed in any one of claims 1 to 4, wherein R¹ represents a 4-methyl-cyclohexyl group.

7. Benzenesulphonyl-ureas as claimed in any one of claims 1 to 6, wherein "phenylene" is an unsubstituted paraphenylene group.

8. Benzenesulphonyl-ureas as claimed in any one of claims 1 to 7, wherein Y represents a dimethylene group.

9. N - [4 - (β - <2 - isoamyloxy - 5 - methyl - benzamido> - ethyl) - ben- zenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea.

10. N - [4 - (β - <2 - phenoxy - benzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea.



11. N - [4 - (β - $\langle$ 2 - phenoxy - 5 - methyl - benzamido $\rangle$ - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea.
12. N - [4 - (β - $\langle$ 2 - phenoxy - benzamido $\rangle$ - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea.
- 5 13. N - [4 - (β - $\langle$ 2 - isoamyloxy - 5 - chloro - benzamido $\rangle$ - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea. 5
14. N - [4 - (β - $\langle$ 2 - isoamyloxy - 5 - chloro - benzamido $\rangle$ - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea.
- 10 15. N - [4 - (β - $\langle$ 2 - phenoxy - 4 - chloro - benzamido $\rangle$ - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea. 10
16. N - [4 - (β - $\langle$ 2 - phenoxy - 5 - chloro - benzamido $\rangle$ - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea.
17. N - [4 - (β - $\langle$ 2 - n - amyloxy - 5 - chloro - benzamido $\rangle$ - ethyl) benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea.
- 15 18. Any one of the benzenesulphonyl-ureas as claimed in claim 1 which is described in the Examples herein, other than the compounds claimed in claims 9 to 17. 15
19. Physiologically tolerable salts of any one of the compounds claimed in claims 1 to 18.
- 20 20. A pharmaceutical preparation which comprises a compound as claimed in any one of claims 1 to 19 in admixture or conjunction with a pharmaceutically suitable carrier. 20
21. A pharmaceutical preparation as claimed in claim 20 which contains in dosage unit form from 0.5 to 100 milligrams of the active ingredient.
- 25 22. A pharmaceutical preparation as claimed in claim 20, which contains in dosage unit form from 2 to 10 milligrams of the active ingredient. 25
23. A process for the manufacture of benzenesulphonyl-ureas of the general formula given in claim 1, conducted substantially as described herein.

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* C L M S *

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