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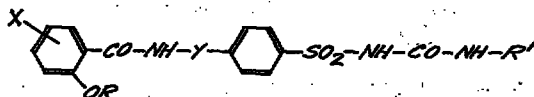


(54) BENZENESULPHONYL-UREAS AND PROCESS FOR
 PREPARING THEM

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

The present invention is concerned with new benzenesulphonyl-ureas and with their manufacture and use.

The present invention provides benzenesulphonyl-ureas of the general formula



which as such or in form of their physiologically tolerable salts show hypoglycemic properties and are characterized by a strong hypoglycemic action. In the general formula:

R represents a lower alkyl group, preferably a methyl group, or a lower alkenyl group,
 X represents a lower acyl, nitro, trifluoromethyl, cyano, methylmercapto, phenyl or benzyl group,

Y represents $-\text{CH}_2\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-\text{CH}_2-$ or $-\text{CH}_2-\text{CH}(\text{CH}_3)-$, and

R¹ represents

- a) an alkyl or alkenyl group each containing 3 to 6 carbon atoms,
- b) a phenyl-lower alkyl group,
- c) a cyclohexyl-lower alkyl, cycloheptyl-methyl, cycloheptyl-ethyl or cyclooctyl-methyl group,
- d) an endoalkylene-cyclohexyl, endoalkylene-cyclohexenyl, endoalkylene-cyclohexylmethyl or endoalkylene-cyclohexenylmethyl group containing 1 or 2 endoalkylene carbon atoms,
- e) a lower alkyl-cyclohexyl or lower alkoxy-cyclohexyl group,
- f) a cycloalkyl group containing 5 to 8 carbon atoms, or
- g) a cyclohexenyl group or a cyclohexenyl-methyl group,

the X substituent being in the 4- or, preferably, the 5-position in the benzene ring with respect to the carbonamide group, the OR substituent being in the 2-position.

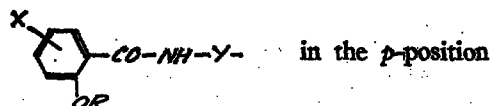
The term "lower" in qualifying alkyl, alkenyl, alkoxy and acyl groups is used herein to mean those groups containing up to 4 carbon atoms in a straight or branched chain.

According to the above-mentioned definitions R may represent, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.butyl or allyl.

R^1 may represent, for example, propyl, isopropyl, butyl, isobutyl, sec.butyl, straight-chained or branched amyl (pentyl), hexyl or allyl, and also benzyl, α -phenylethyl or β -phenylethyl. Of the compounds of the present invention there are especially preferred those compounds in which R^1 represents a cycloaliphatic hydrocarbon group which may be substituted by alkyl or alkoxy (that is as defined in paragraphs (c) to (g) above). Such groups are, for example: cyclopentyl, cyclohexyl, cycloheptyl, cyclo-octyl, methylcyclohexyl, ethyl-cyclohexyl, methoxy-cyclohexyl, ethoxy-cyclohexyl, the alkyl or alkoxy groups being present in the 2-, 3- or, preferably, 4-position, as well as being in the cis- or trans-position, cyclohexyl-methyl, α - or β -cyclohexylethyl, endomethylene-cyclohexyl (2,2,1-bicycloheptyl), endoethylene-cyclohexyl (2,2,2-bicyclo-octyl), endomethylene-cyclohexenyl, endoethylene-cyclohexenyl, endomethylene-cyclohexyl-methyl, endoethylene-cyclohexyl-methyl, endomethylene-cyclohexenyl-methyl or endoethylene-cyclohexenyl-methyl.

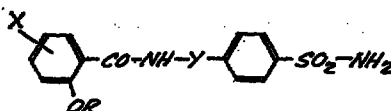
The present invention also provides a process for the preparation of the benzenesulphonyl-ureas as defined above or salts thereof, wherein

- a) a benzenesulphonyl-isocyanate, benzenesulphonyl-carbamic acid ester, benzenesulphonyl-thiocarbamic acid ester, benzenesulphonyl-carbamic acid halide, benzenesulphonyl-urea, benzenesulphonyl-semicarbazide or benzenesulphonyl-semicarbazone which is substituted by a group of the formula



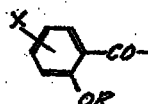
is reacted with an amine, R^1-NH_2 , or, if desired, a salt thereof,

- b) a sulphonamide of the formula

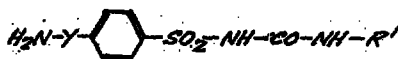


or a salt thereof is reacted with an R^1 -isocyanate, or R^1 -substituted-carbamic acid ester, -thiocarbamic acid ester, -carbamic acid halide or -urea,

- c) a correspondingly substituted benzenesulphonyl-isourea ether, benzenesulphonyl-isourea ester, benzenesulphonyl-isothiurea ether, benzenesulphonyl-parabanic acid or benzenesulphonyl-haloformic acid amidine is hydrolysed,
 d) a correspondingly substituted benzenesulphonyl-halide is reacted with an R^1 -substituted urea or a salt thereof,
 e) a correspondingly substituted benzenesulphinic acid halide, or (in the presence of an acid condensing agent) a correspondingly substituted benzenesulphinic acid or an alkali metal salt thereof, is reacted with a hydroxy-urea, the NH_2 - group of which is substituted by a group represented by R^1 ,
 f) water is added on to a correspondingly substituted carbodiimide,
 g) the sulphur atom is replaced by an oxygen atom in a correspondingly substituted benzenesulphonyl-thiourea,
 h) a correspondingly substituted benzenesulphenyl-urea or benzenesulphenyl-urea is oxidized,
 i) a corresponding benzenesulphonyl-urea containing an unsaturated bond in the molecule is hydrogenated,
 j) a group of the formula

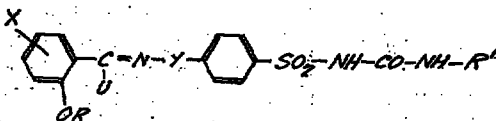


is introduced by acylation, if desired, stepwise, into a benzenesulphonyl-urea of the formula

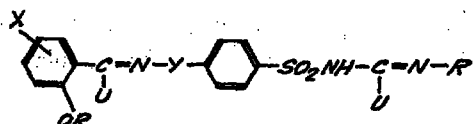


- k) in a correspondingly substituted thiobenzamido-alkylbenzenesulphonyl-urea or thio-

benzamido-alkylbenzenesulphonyl-thiourea the sulphur atom or the sulphur atoms is/are replaced by an oxygen atom or oxygen atoms, respectively, or
1) a compound of the formula



or a parabanic acid derivative thereof or a compound of the formula



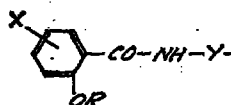
in which each U represents an -O-lower alkyl or -S-lower alkyl group or a halogen atom (preferably a chlorine atom), is saponified.

The above-mentioned benzenesulphonyl-carbamic acid esters or the benzenesulphonyl-thiolcarbamic acid esters may contain in the alcohol component an alkyl group, an aryl group or a heterocyclic group. Since this group is split off during the reaction its chemical constitution has no influence on the nature of the end-product and may therefore vary within wide limits. The same applies to the R¹-substituted carbamic acid esters or the corresponding thiolcarbamic acid esters.

As the carbamic acid halides there are primarily used the chlorides.

The benzenesulphonyl-ureas used as starting materials for 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- or especially di-substituted. Since these substituents are split off during the reaction with amines, their nature can vary within wide limits. Besides benzenesulphonyl-urea substituted by an alkyl, aryl, acyl or heterocyclic group, there can likewise be used bis-(benzenesulphonyl)-ureas, which may carry a further substituent at one of the nitrogen atoms, for example a methyl group. It is, for example, possible to treat such bis-(benzenesulphonyl)-ureas or N-benzenesulphonyl-N'-acyl-ureas with R¹-substituted amines and to heat the salts 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 from such ureas which are mono- or, in particular, di-substituted at the free nitrogen atom and to react these with benzenesulphonamides para-substituted by the group of the formula



As such starting materials there may be mentioned, for example, N-cyclohexyl-ureas or N-(4-methyl-cyclohexyl)-ureas, the corresponding N'-acetyl-ureas, N'-nitro-ureas, N'-cyclohexyl-ureas, N'-(4-methyl-cyclohexyl)-ureas, N',N'-diphenyl-ureas (in which the phenyl groups may each also be substituted and/or may be linked with one another directly or by means of a bridge member such as -CH₂-, -NH-, -O- or -S-), N'-methyl-N'-phenyl-ureas and N',N'-dicyclohexyl-ureas as well as Y-substituted-cyclohexyl-carbamoyl-imidazoles or -cyclohexyl-carbamoyl-triazoles.

Hydrolysis of the mentioned benzenesulphonyl-parabanic acids, benzenesulphonyl-isourea-ethers, benzenesulphonyl-isothioureas, benzenesulphonyl-isourea-esters or benzenesulphonyl-haloformic acid amidines is preferably carried out in an alkaline medium. Isourea-ethers and isourea-esters can also be hydrolysed successfully in an acid medium.

The reaction of the benzenesulphohalides with R¹-substituted ureas is preferably carried out in the presence of strong basic condensing agents, such as alkali metals, alkali metal amides or, preferably, alkali metal hydrides in inert solvents.

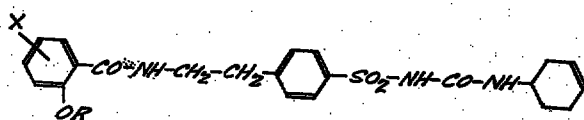
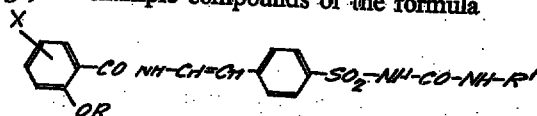
The reaction of sulphinic acids or sulphinic acid chlorides with hydroxy ureas may preferably be effected in inert solvents. When choosing as starting materials the sulphinic acids or the alkali metal salts thereof, acid condensing agents such as thionyl chloride, polyphosphoric acids, anhydrous phosphoric acid or sulphuric acid must be added.

The sulphur atom of the thioureas in correspondingly substituted benzenesulphonyl-thioureas can be replaced by an oxygen atom in a known manner, for example with the aid of oxides or salts or heavy metals or also by using oxidizing agents such as hydrogen peroxide, sodium peroxide or nitrous acid.

Thioureas may also be desulphurized by treating them with phosgene or phosphorus pentachloride. Chloroformic acid-amidines or carbodiimides obtained as intermediate products can be converted into the benzenesulphonyl-ureas by suitable methods, such as, for example by saponification or the addition of water.

The oxidation of the benzenesulphinyl ureas or the benzenesulphenyl ureas may be carried out in inert solvents with known oxidizing agents, such as, for example, potassium permanganate.

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



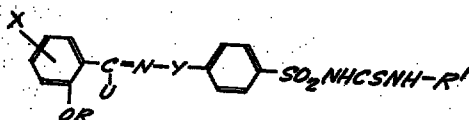
can be converted by hydrogenation, for example with molecular hydrogen, in the presence of a known hydrogenation catalyst into the benzenesulphonyl-ureas of the present invention.

The acylation of aminoalkyl-benzenesulphonyl-ureas may be carried out either in one step, for example by reaction with correspondingly substituted benzoic acid halides, or it may be carried out in several steps.

The sulphur atoms in correspondingly substituted thiobenzamidoalkyl-benzenesulphonyl-ureas or thiobenzamidoalkyl-benzenesulphonyl-thioureas can be replaced by oxygen atoms, for example, with the aid of oxidizing agents such as hydrogen peroxide, sodium peroxide or other peroxide compounds.

Instead of the thiobenzamidoalkyl-benzenesulphonyl-ureas, the corresponding thiobenzamidoalkyl-benzenesulphonyl-isothiourea-ethers, -isourea-ethers or -isourea-esters, thiobenzamidoalkyl-benzenesulphonyl-parabanic acids or thiobenzamidoalkyl-benzenesulphonyl-haloformic acid amidines can be desulphurized by treatment with oxidizing agents in an acid or alkaline medium whereby a hydrolysis forming the sulphonyl-urea grouping simultaneously occurs, thus yielding the benzamidoalkyl-benzenesulphonyl-ureas.

Instead of the thiobenzamidoalkyl-benzenesulphonyl-thioureas, compounds of the formula

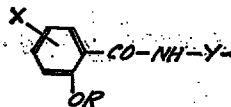


in which U has the meaning given above, can be converted by treatment with oxidizing agents in an acid or alkaline medium by simultaneous desulphuration and hydrolysis into the benzamidoalkyl-benzenesulphonyl-ureas.

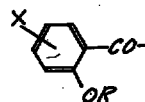
As regards the reaction conditions, the manner of carrying out the process of the present invention may, in general, vary within wide limits and can be adapted to each individual case. For example, the reactions of the present invention can be carried out with or without solvents and either at room temperature or at elevated temperature.

It depends on the nature of the starting materials whether in individual cases one or another of the methods defined above leads to a desired individual benzenesulphonyl-urea in only a low yield, or whether it is not suitable at all to obtain the desired benzenesulphonyl-ureas. In such cases, which occur relatively rarely, the expert has no difficulty in synthesizing the desired product by one or another of the defined methods.

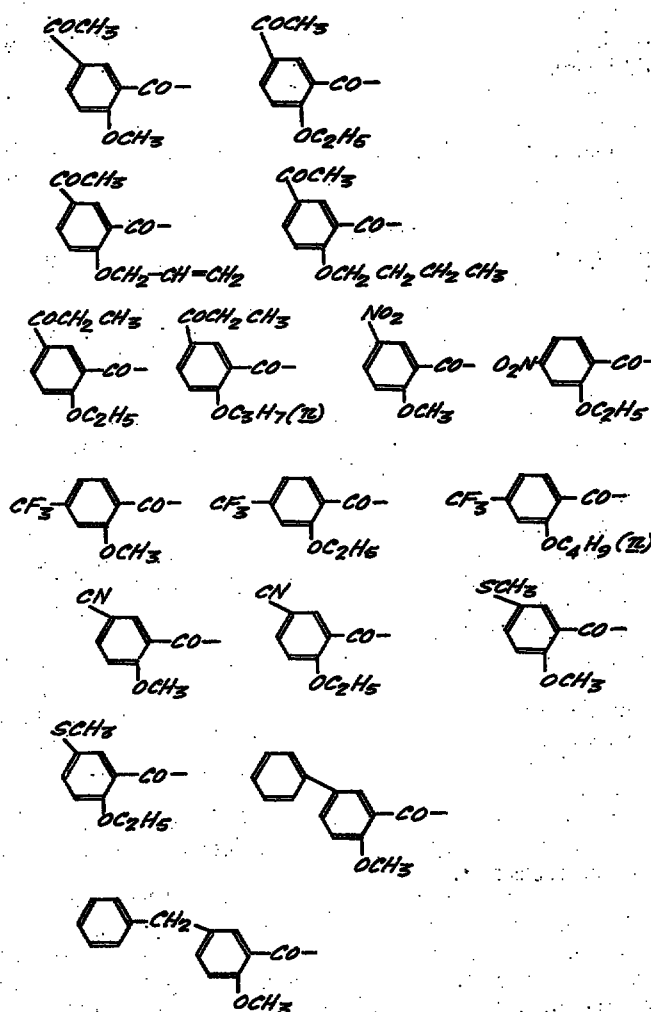
As starting materials such compounds are used that contain a benzene group substituted by a group of the formula



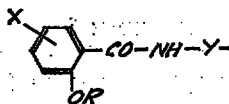
Among examples of the part



of this formula, there may be mentioned the following groups:



The starting materials are prepared according to generally known methods. Thus, for example, the benzenesulphonamides which are used as starting materials and which are para-substituted in the benzene nucleus by the group of the formula



can be obtained by reacting the corresponding benzene compounds with chlorosulphonic

acid and subsequently with ammonia or by acylating the amino compounds of the formula



with the corresponding acid chlorides.

Benzenesulphonyl-carbamic acid esters and benzenesulphonyl-ureas which are used as starting materials may be obtained, for example, from benzenesulphonamides and haloformic acid alkyl esters or potassium cyanate (KOCN).

The hypoglycemic action of the benzenesulphonyl-ureas of the present invention can be determined by feeding them to rabbits in doses of 10 mg/kg of body weight and determining the blood sugar value according to the known method by Hagedorn-Jensen or by means of an autoanalyzer over a prolonged period of time.

Thus, it is found, for example, that 10 mg/kg of body weight of N-[4-(β<2-methoxy-4-trifluoromethyl-benzamido>-ethyl)-benzenesulphonyl]-N'-(4-methyl-cyclohexyl)-urea provokes, after 3 hours, a lowering of the blood sugar by 16%, which lowering, even after 24 hours, still amounts to 25% and which falls to zero only after 48 hours.

In the same manner, 10 mg/kg of N-[4-(β<2-ethoxy-5-acetyl-benzamido>-ethyl)-benzenesulphonyl]-N'-(4-methylcyclohexyl)-urea provokes after 3 hours a lowering of the blood sugar by 32%, which lowering after 24 hours still amounts to 21%, whereas the hitherto known N-[4-methyl-benzenesulphonyl]-N'-butyl-urea, when administered to rabbits in doses of less than 25 mg/kg of body weight, does not provoke a lowering of the blood sugar level.

The strong hypoglycemic action of the benzenesulphonyl-ureas of the present invention becomes more evident if the dose is further reduced. When N-[4-(β<2-methoxy-5-acetyl-benzamido>-ethyl)-benzenesulphonyl]-N'-(4-methyl-cyclohexyl)-urea is administered to rabbits in a dose of 0.2 mg/kg of body weight N-[4-(β<2-methoxy-4-trifluoromethyl-benzamidoethyl)-benzenesulphonyl]-N'-cyclohexyl-urea is administered to rabbits in a dose of 0.1 mg/kg of body weight, and N-[4-(β<2-methoxy-4-trifluoromethyl-benzamido>-ethyl)-benzenesulphonyl]-N'-(4-methyl-cyclohexyl)-urea is administered to rabbits in a dose of 0.08 mg/kg of body weight, a distinct lowering of the blood sugar level can in each case still be observed.

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

The new benzenesulphonyl-ureas are preferably used for the manufacture of orally administrable pharmaceutical preparations for the lowering of the blood sugar level in the treatment of diabetes mellitus; they may be used as such or in the form of their physiologically tolerable salts or in the presence of substances which cause such salt formation. For the formation of salts there may be used, for example, bases such as alkali metal hydroxides or alkaline earth metal hydroxides, alkali metal carbonates or bicarbonates or alkaline earth metal carbonates or bicarbonates.

The pharmaceutical preparations are advantageously in the form of tablets containing, in addition to the aforesaid compounds of the present invention, the usual pharmaceutically suitable auxiliary agents and carriers such as talc, starch, lactose, tragacanth or magnesium stearate.

A pharmaceutical preparation containing the aforesaid benzenesulphonyl-ureas or physiologically tolerable salt thereof as the active substance, for example a tablet or a powder, with or without the aforesaid additives, is advantageously brought into a suitable unit dosage form. The dose chosen should comply with the activity of the benzenesulphonyl-urea used and the desired effect. Advantageously, the dosage per unit amounts to 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-ethoxy-5-acetylbenzamido>-ethyl)-benzenesulphonyl]-N'-(4-methylcyclohexyl)-urea (trans)

8 g of 4-(β<2-ethoxy-5-acetylbenzamido>-ethyl)-benzenesulphonamide (melting point: 197—198°C.; obtained from 2-ethoxy-5-acetyl-benzoic acid and 4-(β-amino-

ethyl)-benzenesulphonamide) were dissolved in 10.5 ml of 2N sodium hydroxide solution and 40 ml of acetone and 3.1 g of 4-methylcyclohexyl-isocyanate (trans) were added dropwise while stirring at 0–5°C. Stirring was continued for 3 hours at room temperature, the whole was then diluted with water and methanol, any undissolved matter was filtered off, and the filtrate was acidified with dilute hydrochloric acid. The resulting N-[4-(β-|<2-ethoxy-5-acetylbenzamido>-ethyl)-benzenesulphonyl]-N'-(4-methylcyclohexyl)-urea (trans) obtained in a crystalline form melted at 162–164°C. after recrystallization from methanol.

In an analogous manner there was obtained N-[4-(β-|<2-ethoxy-5-acetylbenzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea melting at 161–162°C. (from methanol).

In an analogous manner there was obtained:

from 4-(β-|<2-methoxy-5-propionylbenzamido>-ethyl)-benzenesulphonamide (melting point: 203–205°C.): N-[4-(β-|<2-methoxy-5-propionylbenzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea, melting at 136–138°C. (from methanol) and

N-[4-(β-|<2-methoxy-5-propionylbenzamido>-ethyl)-benzenesulphonyl]-N'-(4-methylcyclohexyl)-urea (trans), melting at 137–139°C. (from methanol);

from 4-(β-|<2-allyloxy-5-acetylbenzamido>-ethyl)-benzenesulphonamide (melting point 169–171°C.): N-[4-(β-|<2-allyloxy-5-acetylbenzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea, melting at 154–155°C. (from methanol) and

N-[4-(β-|<2-allyloxy-5-acetylbenzamido>-ethyl)-benzenesulphonyl]-N'-(4-methylcyclohexyl)-urea (trans), melting at 143–145°C. (from methanol);

from 4-(β-|<2-methoxy-4-trifluoromethylbenzamido>-ethyl)-benzenesulphonamide (melting point 172–174°C.): N-[4-(β-|<2-methoxy-4-trifluoromethylbenzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea, melting at 182–183°C. (from methanol) and

N-[4-(β-|<2-methoxy-4-trifluoromethylbenzamido>-ethyl)-benzenesulphonyl]-N'-(4-methylcyclohexyl)-urea (trans) melting at 191–193°C. (from methanol);

from 4-(β-|<2-methoxy-5-phenylbenzamido>-ethyl)-benzenesulphonamide (melting point: 213–214°C.): N-[4-(β-|<2-methoxy-5-phenylbenzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea, melting at 194–195°C. (from methanol/dimethylformamide),

N-[4-(β-|<2-methoxy-5-phenylbenzamido>-ethyl)-benzenesulphonyl]-N'-(4-methylcyclohexyl)-urea (trans) melting at 189–190°C. (from methanol/dimethylformamide) and

N-[4-(β-|<2-methoxy-5-phenylbenzamido>-ethyl)-benzenesulphonyl]-N'-(4-ethylcyclohexyl)-urea (trans), melting at 183–184°C. (from methanol);

from 4-(β-|<2-methoxy-5-benzylbenzamido>-ethyl)-benzenesulphonamide (melting point 158–160°C.): N-[4-(β-|<2-methoxy-5-benzylbenzamido>-ethyl)-benzenesulphonyl]-N'-(4-methylcyclohexyl)-urea (trans) melting at 150–151°C. (from methanol);

from 4-(β-|<2-methoxy-4-nitrobenzamido>-ethyl)-benzenesulphonamide (melting point 207–209°C.): N-[4-(β-|<2-methoxy-4-nitrobenzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea, melting at 196–198°C. (from methanol),

N-[4-(β-|<2-methoxy-4-nitrobenzamido>-ethyl)-benzenesulphonyl]-N'-(4-methylcyclohexyl)-urea (trans) melting at 197–198°C. (from methanol) and

N-[4-(β-|<2-methoxy-4-nitrobenzamido>-ethyl)-benzenesulphonyl]-N'-(4-ethylcyclohexyl)-urea (trans) melting at 201–202°C. (from methanol/dimethylformamide);

from 4-(β-|<2-ethoxy-4-nitrobenzamido>-ethyl)-benzenesulphonamide (melting point 213°C.): N-[4-(β-|<2-ethoxy-4-nitrobenzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea, melting at 174–176°C. (from methanol) and

N-[4-(β-|<2-ethoxy-4-nitrobenzamido>-ethyl)-benzenesulphonyl]-N'-(4-methylcyclohexyl)-urea (trans) melting at 195–197°C. (from methanol/dimethylformamide);

from 4-(β-|<2-methoxy-5-nitrobenzamido>-ethyl)-benzenesulphonamide (melting point 174–176°C.): N-[4-(β-|<2-methoxy-5-nitrobenzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea, melting at 146–148°C. (from methanol) and

N-[4-(β-|<2-methoxy-5-nitrobenzamido>-ethyl)-benzenesulphonyl]-

- 17
- 5 N'-(4-methylcyclohexyl)-urea (trans) melting at 163—164°C. (from methanol);
from 4 - (β - <2 - ethoxy - 4 - trifluoromethylbenzamido> - ethyl) - benzene-
sulphonamide (melting point 228—229°C.): N - [4 - (β - <2 - ethoxy - 4 - trifluoromethylbenzamido> - ethyl) - benzenesulphonyl] - N'-(β-phenylethyl)-urea, melting
at 148—149°C. (from methanol),
- 10 N - [4 - (β - <2 - ethoxy - 4 - trifluoromethylbenzamido> - ethyl) - benzene-
sulphonyl] - N'-cyclohexylmethyl-urea, melting at 194—195°C. (from methanol),
N - [4 - (β - <2 - ethoxy - 4 - trifluoromethylbenzamido> - ethyl) - benzene-
sulphonyl] - N'-cyclopentyl-urea, melting at 143—144°C. (from methanol),
- 15 N - [4 - (β - <2 - ethoxy - 4 - trifluoromethylbenzamido> - ethyl) - benzene-
sulphonyl] - N'-(4-isopropoxycyclohexyl)-urea, melting at 184—185°C. (from
methanol),
N - [4 - (β - <2 - ethoxy - 4 - trifluoromethylbenzamido> - ethyl) - benzene-
sulphonyl] - N'-n-hexyl-urea, melting at 173—174°C. (from methanol) and
- 20 N - [4 - (β - <2 - ethoxy - 4 - trifluoromethylbenzamido> - ethyl) - benzene-
sulphonyl] - N'-cyclo-heptyl-urea, melting at 162—164°C. (from methanol);
from 4 - (β - <2 - methoxy - 5 - trifluoromethylbenzamido> - ethyl) - benzene-
sulphonamide melting point 198°C.): N - [4 - (β - <2 - methoxy - 5 - tri-
fluoromethylbenzamido> - ethyl) - benzenesulphonyl] - N'-cyclohexyl-urea, melting
at 106°C. (with decomposition) (from methanol),
- 25 N - [4 - (β - <2 - methoxy - 5 - trifluoromethylbenzamido> - ethyl) - benzene-
sulphonyl] - N'-butyl-urea, melting at 123—125°C. (from methanol),
N - [4 - (β - <2 - methoxy - 5 - trifluoromethylbenzamido> - ethyl) - benzene-
sulphonyl] - N'-(4-methylcyclohexyl)-urea (trans) melting at 168—170°C. (from
methanol) and
- 30 N - [4 - (β - <2 - methoxy - 5 - trifluoromethylbenzamido> - ethyl) - benzene-
sulphonyl] - N'-cycloheptyl-urea, melting at 104—106°C. (from methanol);
from 4 - (β - <2 - ethoxy - 5 - trifluoromethylbenzamido> - ethyl) - benzene-
sulphonamide (melting point 200°C.): N - [4 - (β - <2 - ethoxy - 5 - trifluoro-
methylbenzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea, melting
at 140—142°C. (from methanol) and
- 35 N - [4 - (β - <2 - ethoxy - 5 - trifluoromethylbenzamido> - ethyl) - benzene-
sulphonyl] - N'-(4-methylcyclohexyl)-urea, (trans) melting at 170—171°C. (from
methanol);
from 4 - (β - <2 - ethoxy - 5 - nitrobenzamido> - ethyl) - benzenesulphon-
amide (melting point 178—180°C.): N - [4 - (β - <2 - ethoxy - 5 - nitrobenz-
amido> - ethyl) - benzenesulphonyl] - N' - (4 - methylcyclohexyl) - urea (trans)
melting at 169—170°C. (from methanol);
- 40 from 4 - (β - <2 - ethoxy - 4 - trifluoromethyl - benzamido> - ethyl) - benzene-
sulphonamide (melting point 228—229°C.): N - [4 - (β - <2 - ethoxy - 4 - tri-
fluoromethylbenzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea,
melting at 172—174°C. (from methanol),
N - [4 - (β - <2 - ethoxy - 4 - trifluoromethylbenzamido> - ethyl) - benzene-
sulphonyl] - N'-butyl-urea, melting at 151—153°C. (from methanol) and
- 45 N - [4 - (β - <2 - ethoxy - 4 - trifluoromethylbenzamido> - ethyl) - benzene-
sulphonyl] - N'-(4-methylcyclohexyl)-urea (trans) melting at 185—186°C.;
from 4 - (β - <2 - n - propoxy - 5 - acetylbenzamido> - ethyl) - benzenesulphon-
amide (melting point: 201—202°C.): N - [4 - (β - <2 - n - propoxy - 5 -
acetylbenzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methylcyclohexyl) - urea
(trans) melting at 121—123°C. (from methanol), and
- 50 from 4 - (β - <2 - n - butoxy - 5 - acetylbenzamido> - ethyl) - benzenesulphon-
amide (melting point 187—188°C.): N - [4 - (β - <2 - n - butoxy - 5 - acetyl-
benzamido> - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea, melting at
169—170°C. (from methanol).
- 55 **EXAMPLE 2**
N - [4 - (β - <2 - methoxy - 5 - acetylbenzamido> - ethyl) - benzenesulphonyl] -
N'-(4-methylcyclohexyl)-urea (trans)
- 60 8.7 g of N - [4 - (β - <2 - methoxy - 5 - acetylbenzamido> - ethyl) -
benzenesulphonyl] - methyl - urethane (melting point: 190—192°C.), obtained
by the reaction of 4 - (β - <2 - methoxy - 5 - acetylbenzamido> - ethyl) -
benzenesulphonamide (melting point: 206—208°C.) with chloroformic acid methyl
ester, were suspended in 100 ml of dioxan. After the addition of 2.3 g of methylcyclo-
hexyl amine (trans) the whole was heated for 90 minutes at 110°C., whereby the

methanol which had formed during the reaction was distilled off. The sulphonyl-urea named in the heading was obtained in the form of crystals by the addition of a small quantity of water to the cooled reaction mixture. After recrystallization from methanol, its melting point was 155—157°C.

In an analogous manner there was obtained:

N - [4 - (β - <2 - methoxy - 5 - acetylbenzamido> - ethyl) - benzenesulphonyl] - N'-cyclohexyl-urea, melting at 162—163°C. (from methanol),

N - [4 - (β - <2 - methoxy - 5 - acetylbenzamido> - ethyl) - benzenesulphonyl] - N'-butyl-urea, melting at 158—160°C. (from methanol) and

N - [4 - (β - <2 - methoxy - 5 - acetylbenzamido> - ethyl) - benzenesulphonyl] - N'-isobutyl-urea, melting at 160—162°C. (from methanol);

from N - [4 - (β - <2 - methoxy - 4 - trifluoromethylbenzamido> - ethyl) - benzenesulphonyl] - methyl - urethane (melting point: 190—192°C.): N - [4 - (β - <2 - methoxy - 4 - trifluoromethylbenzamido> - ethyl) - benzenesulphonyl] - N'-butyl-urea, melting at 159—161°C. (from methanol),

N - [4 - (β - <2 - methoxy - 4 - trifluoromethylbenzamido> - ethyl) - benzenesulphonyl] - N' - (4 - methoxy - cyclohexyl) - urea, melting at 170—172°C. (from methanol),

N - [4 - (β - <2 - methoxy - 4 - trifluoromethylbenzamido> - ethyl) - benzenesulphonyl] - N'-*n*-hexyl-urea, melting at 147—148°C. (from methanol),

N - [4 - (β - <2 - methoxy - 4 - trifluoromethylbenzamido> - ethyl) - benzenesulphonyl] - N'-(3-methylcyclohexyl)-urea, melting at 158—160°C. (from methanol) and

N - [4 - (β - <2 - methoxy - 4 - trifluoromethylbenzamido> - ethyl) - benzenesulphonyl] - N'-(2,5-endomethylenecyclohexyl)-urea, melting at 146—148°C. (from methanol).

EXAMPLE 3

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

a) 2.7 g of N - [4 - (β - <2 - methoxy - 5 - acetyl - benzamido> - ethyl) - benzenesulphonyl] - N'-(β -phenyl-ethyl)-thiourea were dissolved in a mixture of 150 ml of methanol and 40 ml of dimethylformamide. 1.08 g of mercury oxide were added and the whole was stirred while heating for 90 minutes at 60°C. After filtering off the mercury sulphide which had formed, the remainder was mixed with water.

A resinous precipitate of N - [4 - (β - <2 - methoxy - 5 - acetylbenzamido> - ethyl) - benzenesulphonyl] - N'-(β -phenylethyl)-isourea-methyl ether was obtained.

b) The resin obtained as described under paragraph (a) was dissolved in a small amount of dioxan, 2N sodium hydroxide solution was added and the whole was heated for 25 minutes on a steam bath. The batch was cooled, diluted with water and acidified.

The resulting N - [4 - (β - <2 - methoxy - 5 - acetyl - benzamido> - ethyl) - benzenesulphonyl] - N'-(β -phenylethyl)-urea was obtained as a crystalline precipitate melting, after recrystallization from methanol, at 144—146°C.

EXAMPLE 4

N - [4 - (β - <2 - methoxy - 5 - acetyl> - benzamido - ethyl) - benzenesulphonyl] - N-(β -phenyl-ethyl)-urea

6.5 g of N - [4 - (β - <2 - methoxy - 5 - acetyl - benzamido> - ethyl) - benzenesulphonyl] - N'-(β -phenylethyl)-thiourea (prepared by boiling the corresponding sulphonamide with phenylethyl mustard oil in acetone in the presence of potassium carbonate, melting point 195—197°C. with decomposition from dilute methanol) were suspended in 250 ml of acetone. Then, 2.07 g of sodium nitrite dissolved in little water were added, and then 20 ml of 5N acetic acid were added dropwise while stirring and cooling with ice and stirring was continued for 2½ hours at room temperature. After filtering and distilling off the acetone, the residue was dissolved in dilute ammonia, filtered over carbon and the filtrate was acidified. An oily precipitate of N - [4 - (β - <2 - methoxy - 5 - acetyl> - benzamidoethyl) - benzenesulphonyl] - N'-(β -phenylethyl)-urea was obtained which crystallized from methanol. The substance thus purified melted at 144—146°C.

EXAMPLE 5

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

4.1 g of 4-(β -<2-ethoxy-5-acetyl-benzamido)-ethyl-benzenesulphonamide-

sodium and 4.4 g of N-cyclohexyl-carbamic acid phenyl ester were dissolved in 100 ml of dimethyl formamide. The solution was heated for 45 minutes at 110°C.; after cooling, aqueous ammonia of 0.5% strength was added, the resulting solution was filtered and the filtrate was acidified. The resulting precipitate was filtered with suction and recrystallized from methanol. The N-[4-(β-<2-ethoxy-5-acetylbenzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea so obtained melted at 161-162°C.

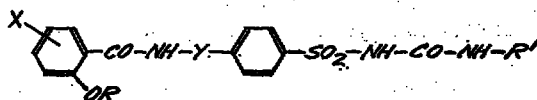
EXAMPLE 6

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

4.1 g of 4 - (β - <2 - methoxy - 5 - propionyl - benzamido> - ethyl)-benzenesulphonamide-sodium were heated with 5.9 g of N,N-diphenyl-N'-cyclohexyl-urea in 100 ml of dimethyl formamide for 45 minutes at 110°C. After cooling, the whole was treated with ammonia of about 0.5% strength, filtered and the filtrate was acidified. The precipitate so obtained was once again dissolved and precipitated from ammonia of 0.5% strength and then recrystallized from methanol. The resulting N-[4 - (β - <2 - methoxy - 5 - propionyl - benzamido> - ethyl) - benzenesulphonyl]-N'-cyclohexyl-urea melted at 136-138°C.

WHAT WE CLAIM IS:—

1. A benzenesulphonyl-urea of the general formula



in which

R represents a lower alkyl or lower alkenyl group,

R¹ represents

- an alkyl or alkenyl group each containing 3 to 6 carbon atoms,
- a phenyl-lower alkyl group,
- a cyclohexyl-lower alkyl, cycloheptyl-methyl, cycloheptyl-ethyl or cyclooctyl-methyl group,
- an endoalkylene-cyclohexyl, endoalkylene-cyclohexenyl, endoalkylene-cyclohexylmethyl or endoalkylene-cyclohexenylmethyl group containing 1 or 2 endoalkylene carbon atoms,
- a lower alkyl-cyclohexyl or lower alkoxy-cyclohexyl group,
- a cycloalkyl group containing 5 to 8 carbon atoms, or
- a cyclohexenyl group or a cyclohexenyl-methyl group,

X represents a lower acyl, nitro, trifluoromethyl, cyano, methylmercapto, phenyl or benzyl group the X substituent being in the 4- or 5-position in the benzene ring with respect to the carbonamide group, the OR substituent being in the 2-position, and

Y represents —CH₂—CH₂—, —CH(CH₃)—CH₂— or —CH₂—CH(OH)—.

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

3. A compound as claimed in claim 1, wherein R represents a methyl group.

4. A physiologically tolerable salt of a compound as claimed in claim 3.

5. A compound as claimed in claim 1, wherein X represents a trifluoromethyl in the 5-position, R represents a methyl group, Y represents —CH₂—CH₂— and R¹ represents a cyclohexyl group.

6. A compound as claimed in claim 1, wherein X represents a trifluoromethyl in the 5-position, R represents a methyl group, Y represents —CH₂—CH₂— and R¹ represents a 4-methyl-cyclohexyl (trans) group.

7. A compound as claimed in claim 1, wherein X represents a trifluoromethyl in the 5-position, R represents a methyl group, Y represents —CH₂—CH₂— and R¹ represents a cycloheptyl group.

8. A compound as claimed in claim 1, wherein X represents a trifluoromethyl in the 5-position, R represents an ethyl group, Y represents —CH₂—CH₂— and R¹ represents a cyclohexyl group.

9. A compound as claimed in claim 1, wherein X represents a trifluoromethyl in the 5-position, R represents an ethyl group, Y represents —CH₂—CH₂— and R¹ represents a 4-methyl-cyclohexyl (trans) group.

10. A compound as claimed in claim 1, wherein X represents an acetyl group in the 5-position, R represents an ethyl group, Y represents —CH₂—CH₂— and R¹ represents a 4-methyl-cyclohexyl (trans) group.

sodium and 4.4 g of N-cyclohexyl-carbamic acid phenyl ester were dissolved in 100 ml of dimethyl formamide. The solution was heated for 45 minutes at 110°C.; after cooling, aqueous ammonia of 0.5% strength was added, the resulting solution was filtered and the filtrate was acidified. The resulting precipitate was filtered with suction and recrystallized from methanol. The N-[4-(β-<2-ethoxy-5-acetylbenzamido>-ethyl)-benzenesulphonyl]-N'-cyclohexyl-urea so obtained melted at 161-162°C.

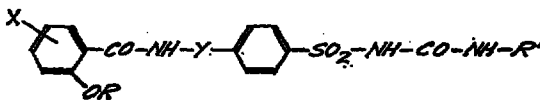
EXAMPLE 6

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

4.1 g of 4 - (β - <2 - methoxy - 5 - propionyl - benzamido> - ethyl) - benzenesulphonamide-sodium were heated with 5.9 g of N,N-diphenyl-N'-cyclohexyl-urea in 100 ml of dimethyl formamide for 45 minutes at 110°C. After cooling, the whole was treated with ammonia of about 0.5% strength, filtered and the filtrate was acidified. The precipitate so obtained was once again dissolved and precipitated from ammonia of 0.5% strength and then recrystallized from methanol. The resulting N-[4 - (β - <2 - methoxy - 5 - propionyl - benzamido> - ethyl) - benzenesulphonyl]-N'-cyclohexyl-urea melted at 136-138°C.

WHAT WE CLAIM IS:—

1. A benzenesulphonyl-urea of the general formula



in which

R represents a lower alkyl or lower alkenyl group,

R¹ represents

- a) an alkyl or alkenyl group each containing 3 to 6 carbon atoms,
- b) a phenyl-lower alkyl group,
- c) a cyclohexyl-lower alkyl, cycloheptyl-methyl, cycloheptyl-ethyl or cyclooctyl-methyl group,
- d) an endoalkylene-cyclohexyl, endoalkylene-cyclohexenyl, endoalkylene-cyclohexylmethyl or endoalkylene-cyclohexenylmethyl group containing 1 or 2 endoalkylene carbon atoms,
- e) a lower alkyl-cyclohexyl or lower alkoxy-cyclohexyl group,
- f) a cycloalkyl group containing 5 to 8 carbon atoms, or
- g) a cyclohexenyl group or a cyclohexenyl-methyl group,

X represents a lower acyl, nitro, trifluoromethyl, cyano, methylmercapto, phenyl or benzyl group the X substituent being in the 4- or 5-position in the benzene ring with respect to the carbonamide group, the OR substituent being in the 2-position, and

Y represents —CH₂—CH₂—, —CH(CH₃)—CH₂— or —CH₂—CH(CH₃)—.

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

3. A compound as claimed in claim 1, wherein R represents a methyl group.

4. A physiologically tolerable salt of a compound as claimed in claim 3.

5. A compound as claimed in claim 1, wherein X represents a trifluoromethyl in the 5-position, R represents a methyl group, Y represents —CH₂—CH₂— and R¹ represents a cyclohexyl group.

6. A compound as claimed in claim 1, wherein X represents a trifluoromethyl in the 5-position, R represents a methyl group, Y represents —CH₂—CH₂— and R¹ represents a 4-methyl-cyclohexyl (trans) group.

7. A compound as claimed in claim 1, wherein X represents a trifluoromethyl in the 5-position, R represents a methyl group, Y represents —CH₂—CH₂— and R¹ represents a cycloheptyl group.

8. A compound as claimed in claim 1, wherein X represents a trifluoromethyl in the 5-position, R represents an ethyl group, Y represents —CH₂—CH₂— and R¹ represents a cyclohexyl group.

9. A compound as claimed in claim 1, wherein X represents a trifluoromethyl in the 5-position, R represents an ethyl group, Y represents —CH₂—CH₂— and R¹ represents a 4-methyl-cyclohexyl (trans) group.

10. A compound as claimed in claim 1, wherein X represents an acetyl group in the 5-position, R represents an ethyl group, Y represents —CH₂—CH₂— and R¹ represents a 4-methyl-cyclohexyl (trans) group.



11. A compound as claimed in claim 1, wherein X represents an acetyl group in the 5-position, R represents an ethyl group, Y represents $-\text{CH}_2-\text{CH}_2-$ and R^1 represents a cyclohexyl group.

12. A compound as claimed in claim 1, wherein X represents a trifluoromethyl group in the 4-position, R represents a methyl group, Y represents $-\text{CH}_2-\text{CH}_2-$ and R^1 represents a cyclohexyl group.

13. A compound as claimed in claim 1, wherein X represents a trifluoromethyl group in the 4-position, R represents a methyl group, Y represents $-\text{CH}_2-\text{CH}_2-$ and R^1 represents a 4-methyl-cyclohexyl (trans) group.

14. A compound as claimed in claim 1, wherein X represents a trifluoromethyl group in the 4-position, R represents an ethyl group, Y represents $-\text{CH}_2-\text{CH}_2-$ and R^1 represents a 4-methyl-cyclohexyl (trans) group.

15. A compound as claimed in claim 1, wherein X represents an acetyl group in the 5-position, R represents an *n*-propyl group, Y represents $-\text{CH}_2-\text{CH}_2-$ and R^1 represents a 4-methyl-cyclohexyl (trans) group.

16. A compound as claimed in claim 1, wherein X represents an acetyl group in the 5-position, R represents an *n*-butyl group, Y represents $-\text{CH}_2-\text{CH}_2-$ and R^1 represents a cyclohexyl group.

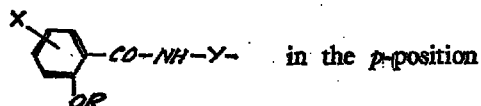
17. A compound as claimed in claim 1, wherein X represents an acetyl group in the 5-position, R represents a methyl group, Y represents $-\text{CH}_2-\text{CH}_2-$ and R^1 represents a 4-methyl-cyclohexyl (trans) group.

18. A physiologically tolerable salt of the compound claimed in any one of claims 5 to 17.

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

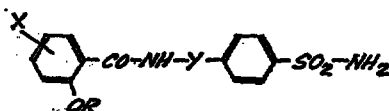
20. A process for the manufacture of a benzenesulphonyl-urea as claimed in claim 1 or a salt thereof, wherein

a) a benzenesulphonyl-isocyanate, benzenesulphonyl-carbamic acid ester, benzenesulphonyl-thiolcarbamic acid ester, benzenesulphonyl carbamic acid halide, benzenesulphonyl-urea or benzenesulphonyl-semicarbazide or -semicarbazone which is substituted by a group of the formula



is reacted with an amine, R^1NH_2 , or a salt thereof,

b) a sulphonamide of the formula



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

c) a correspondingly substituted benzenesulphonyl-isourea ether, benzenesulphonyl-isourea ester, benzenesulphonyl-isothiurea ether, benzenesulphonyl parabanic acid or benzenesulphonyl-haloformic acid amidine is hydrolysed,

d) a correspondingly substituted benzenesulphonyl-halide is reacted with an R^1 -substituted urea or a salt thereof,

e) a correspondingly substituted benzenesulphinic acid halide, or (in the presence of an acid condensing agent) a correspondingly substituted benzenesulphinic acid or an alkali metal salt thereof, is reacted with a hydroxy-urea, the NH_2- group of which is substituted by a group represented by R^1 ,

f) water is added on to a correspondingly substituted carbodiimide,

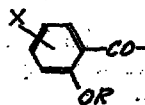
g) the sulphur atom is replaced by an oxygen atom in a correspondingly substituted benzenesulphonyl-thiourea,

h) a correspondingly substituted benzenesulphinyl- or benzenesulphenyl-urea is oxidized,

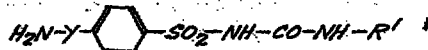
i) a corresponding benzenesulphonyl-urea that contains an unsaturated bond in the molecule is hydrogenated,



j) a group of the formula

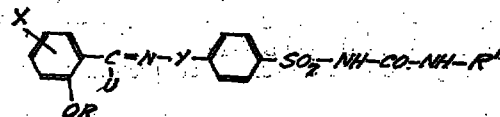


is introduced by acylation, if desired stepwise, into a benzenesulphonyl-urea of the formula

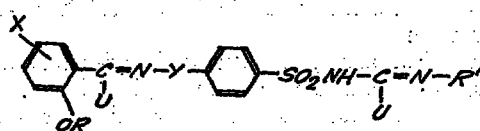


k) in a correspondingly substituted thiobenzamido-alkylbenzenesulphonyl-urea or thiobenzamido-alkylbenzenesulphonyl-thiourea the sulphur atom or atoms is/are replaced by an oxygen atom or by oxygen atoms, respectively, or

l) a compound of the formula



or a parabanic acid derivative thereof, or a compound of the formula



in which each U represents an —O—lower alkyl or —S—lower alkyl group or a halogen atom, is saponified.

21. A process as claimed in claim 20, wherein U represents a chlorine atom.

22. A process as claimed in claim 20, and conducted substantially as described in any one of Examples 1 to 6 herein.

23. A pharmaceutical preparation which comprises a benzenesulphonyl-urea as claimed in claim 1 or 3, in admixture or conjunction with a pharmaceutically suitable carrier.

24. A pharmaceutical preparation which comprises a physiologically tolerable salt as claimed in claim 2 or 4, in admixture or conjunction with a pharmaceutically suitable carrier.

25. A pharmaceutical preparation which comprises the benzenesulphonyl-urea claimed in any one of claims 5 to 17, in admixture or conjunction with a pharmaceutically suitable carrier.

26. A pharmaceutical preparation which comprises a physiologically tolerable salt as claimed in claim 18, in admixture or conjunction with a pharmaceutically suitable carrier.

27. A pharmaceutical preparation as claimed in any one of claims 23 to 26, which is in a form suitable for oral administration.

28. A pharmaceutical preparation as claimed in any one of claims 23 to 27, which is in unit dosage form.

29. A pharmaceutical preparation as claimed in claim 28, containing per unit dose, 0.5 to 100 mg of the benzenesulphonyl-urea or physiologically tolerable salt thereof.

30. A pharmaceutical preparation as claimed in claim 28, containing, per unit dose 2 to 10 mg of the benzenesulphonyl-urea or physiologically tolerable salt thereof.

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