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PATENT SPECIFICATION

NO DRAWINGS

1.106.616

Date of Application and filing Complete Specification: 29 March, 1965.

No. 13221/65.

Application made in Germany (No. F43451 IVb/12o) on 16 July, 1964.

Application made in Luxembourg (No. 47779) on 13 Jan., 1965.

Complete Specification Published: 20 March, 1968.

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Index at acceptance:—C2 C(1J1A3, 1J1A6, 1J1A7, 1J1C2, 1J1C3, 1J12, 2D43B, 2D43F, 2D43J, 2D43L, 2D43S3, 2D43S4, 2D43Z1)

Int. Cl.:—C 07 c 143/82

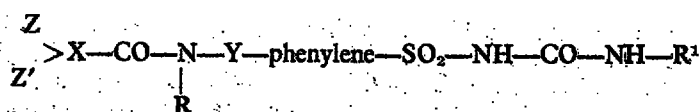
COMPLETE SPECIFICATION

Benzenesulphonyl-Ureas and process for preparing them

We, FARBWERKE HOECHST AKTIENGESSELLSCHAFT, vormalig 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 corresponding to the formula



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

In the above formula the phenylene group is unsubstituted or is substituted by one or more substituents selected from lower alkyl groups, lower alkoxy groups and halogen atoms, and

X represents an aromatic bicyclic hydrocarbon group which may be partially hydrogenated in one ring, and which may be linked to the adjacent carbonyl group by a lower alkylene, lower O-alkylene, lower S-alkylene or $-\text{CH}=\text{CH}-$ group,

Z represents a hydrogen or halogen atom, or a lower alkyl, lower alkoxy or hydroxyl group

Z' represents a hydrogen or halogen atom, or a lower alkyl or lower alkoxy group,

Y represents a straight chain or branched hydrocarbon group containing 1 to 4 carbon atoms,

R represents a hydrogen atom, a lower alkyl group, or a phenyl-lower alkyl group; and

R¹ represents

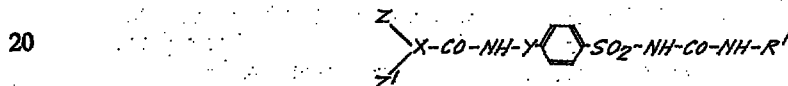
- an alkyl, alkenyl or mercaptoalkyl group containing 2 to 8 carbon atoms,
- an alkoxyalkyl, alkylmercaptoalkyl or alkylsulphinylalkyl group containing 4 to 8 carbon atoms of which at least 2 belong to the alkylene part of the alkoxyalkyl, alkylmercaptoalkyl or alkylsulphinylalkyl group,
- a phenyl-lower alkyl or phenylcyclopropyl group,
- a cyclohexyl-lower alkyl, cycloheptylmethyl, cycloheptylethyl or cyclooctylmethyl group,
- an endoalkylene-cyclohexyl, endoalkylene-cyclohexenyl, endoalkylene-cyclohexylmethyl or endoalkylene-cyclohexenylmethyl group containing 1 or 2 carbon atoms in the endoalkylene part,

[Price 4s. 6d.]

- f) a lower alkyl-cycloalkyl group containing 5 to 8 ring carbon atoms or a lower alkoxy-cyclohexyl group,
 g) a cycloalkyl group containing 5 to 8 carbon atom,
 h) a cyclohexenyl or cyclohexenylmethyl group,
 i) a heterocyclic ring containing 4 or 5 carbon atoms and 1 oxygen atom or 1 sulphur atom and which may also contain up to 2 ethylenic double bonds, or
 k) a heterocyclic ring linked to the adjacent nitrogen atom by means of a methylene group and containing 4 or 5 carbon atoms, 1 oxygen atom or 1 sulphur atom and which may also contain up to 2 ethylenic double bonds.

By the terms "lower alkyl", "lower alkylene", "lower alkoxy", "lower-O-alkylene" and "lower-S-alkylene" groups, there are to be understood herein groups containing 1 to 4 carbon atoms in a straight or branched chain. By the term "lower acyl" group, there is to be understood herein an organic acid acyl group containing up to 4 carbon atoms, preferably a straight chain or branched alkanoyl group of the indicated carbon content.

As examples of the new compounds of the present invention there may be mentioned, for example, more especially benzenesulphonyl-ureas corresponding to the formula



and physiologically tolerable salts thereof, in which

Z represents a hydrogen or halogen atom, or a lower alkyl, lower alkoxy or hydroxyl group,

Z' represents a hydrogen or halogen atom, or a lower alkyl or lower alkoxy group,

X represents an aromatic bicyclic hydrocarbon group which may be partially hydrogenated in one ring, and which is linked to the adjacent carbonyl group by a single chemical bond or by a $-\text{CH}_2-\text{CH}_2-$ or $-\text{O}-\text{CH}_2-$ group,

Y represents a straight chain or branched hydrocarbon group containing 1 to 3 carbon atoms, and

R¹ represents

- an alkyl group containing 3 to 6 carbon atoms,
- a cycloalkyl group containing 5 to 8 carbon atoms,
- a 4-methyl-cyclohexyl group,
- a cyclohexenyl group,
- an endomethylene-cyclohexyl-methyl or endomethylene-cyclohexenyl-methyl group, or
- a cyclohexyl-methyl group.

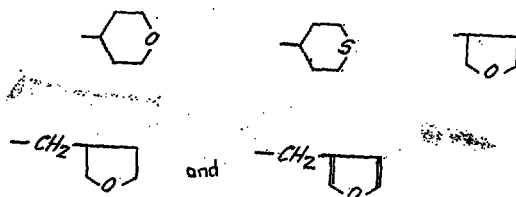
In accordance with the definitions given above, R may represent, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, benzyl, α -phenylethyl, β -phenylether or β - or γ -phenylpropyl. Compounds in which R represents methyl or benzyl and, in particular, those in which R represents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

R¹ may represent, for example, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, straight chain or branched amyl (pentyl), hexyl, heptyl or octyl; the groups with an ethylenic double bond corresponding to the above-mentioned alkyl groups, for example allyl or crotyl, and also alkyl groups containing 2 to 8 carbon atoms and a mercapto group, for example β mercaptoethyl or higher mercaptoalkyl groups. R¹ may also represent, for example, γ -methoxypropyl, δ -methoxy-n-butyl, β -ethoxyethyl, γ -ethoxypropyl, δ -ethoxybutyl or higher alkyloxyethyl, -propyl or -butyl groups containing up to 8 carbon atoms, as well as the corresponding groups in which the oxygen atom is replaced by a sulphur atom or the $-\text{SO}-$ group. Furthermore, R¹ may represent a benzyl, α -phenylethyl, β -phenylethyl, or a α -, β - or γ -phenylpropyl or -phenylbutyl group.

Within the scope of the present invention there are particularly preferred compounds containing as the group represented by R¹, a cycloaliphatic hydrocarbon group as defined in paragraphs (c) to (h) above. Said groups comprise, for example, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, methylcyclohexyl, ethylcyclohexyl, propyl- and isopropyl-cyclohexyl, methoxycyclohexyl, ethoxycyclohexyl, and propoxy- and isopropoxy-cyclohexyl. The alkyl or alkoxy groups may be in the 2-, 3- or, pre-

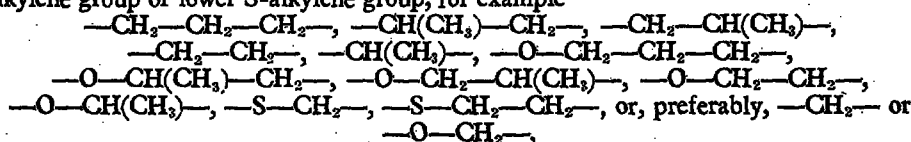
ferably, 4-position, in the cis- as well as in the trans-position. Furthermore, there may be mentioned cyclohexylmethyl, α - or β -cyclohexylethyl, cyclohexylpropyl groups, endomethylene-cyclohexyl (2:2:1-tricycloheptyl), endoethylenecyclohexyl (2:2:2 - tricyclooctyl), endomethylene - cyclohexenyl, endoethylene - cyclohexenyl, endomethylene - cyclohexylmethyl, endoethylene - cyclohexylmethyl, endomethylenecyclohexenylmethyl, endoethylene - cyclohexenylmethyl, or α - or β -phenylcyclopropyl in the cis- as well as in the trans-form.

Finally, R^1 may represent a heterocyclic ring containing 4 or 5 carbon atoms, 1 oxygen or sulphur atom and, if desired, up to 2 double bonds, which heterocyclic ring may be bound to the adjacent nitrogen atom by means of a methylene group. Examples of such heterocyclic rings are



Cyclic systems which enter into consideration as the basic skeleton for the group represented by X in the general formula are, in particular, those containing 8 to 10 carbon atoms, for example naphthalene, indene or benzocyclobutene, or the corresponding systems in which the double bond(s) in one ring which do not form part of the other ring are partially or completely hydrogenated, for example dihydronaphthalene, tetrahydronaphthalene, indane or benzocyclobutane. From among the partially hydrogenated ring systems there are preferred those in which an aromatic nucleus and a saturated cycloaliphatic nucleus are linked with one another.

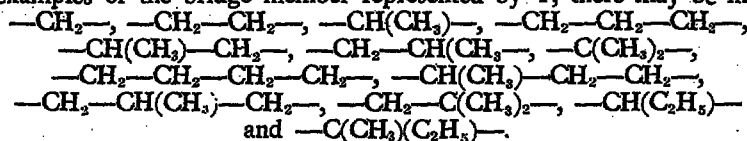
This ring system may be linked to the adjacent carbonyl group in any position. In the case of partially hydrogenated systems the linkage may be in the aromatic as well as in the hydrogenated part of the ring system, a linkage to the aromatic part being preferred. Linkage may also be effected via a lower alkylene group, lower O-alkylene group or lower S-alkylene group, for example



or furthermore via the group $-CH=CH-$.

The substituents represented by Z and Z' may also be linked to the ring system represented by X in any position, for one substituent the ortho-position to the carbonyl group being preferred.

As examples of the bridge member represented by Y, there may be mentioned:



As examples of the substituents represented by Z and Z' there may be mentioned: methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec. butyl and tert. butyl as well as the corresponding alkoxy groups, and fluorine, chlorine bromine and iodine, chlorine being the preferred halogen atom.

The phenylene group indicated in the general formula by -phenylene- is preferably unsubstituted; however, it may also likewise be substituted one or several times by halogen, lower alkyl and/or lower alkoxy. It may contain the remaining parts of the benzenesulphonyl-urea molecule in ortho-, meta- or para-position to one another, the para-position being preferred.

The present invention also provides a process for the manufacture of the aforesaid benzenesulphonyl-ureas, which comprises

(a) reacting a benzenesulphonyl-isocyanate, benzenesulphonyl-carbamic acid ester, benzenesulphonyl-thiocarbamic acid ester, benzenesulphonyl-carbamic acid halide or benzenesulphonyl-urea carrying the substituent $ZZ'-X-CO-NR-Y-$ with an R^1 -substituted amine or a salt thereof; (if a benzenesulphonyl-isocyanate is used in which Z represents OH, this group is protected during the reaction by benzylation or esteri-

fication and is liberated after the reaction by catalytic hydrogenation or saponification), or

(b) reacting a benzenesulphonamide of the formula



5 or a salt thereof with an R¹-substituted isocyanate, carbamic acid ester, thiocarbamic acid ester, carbamic acid halide or urea,

or

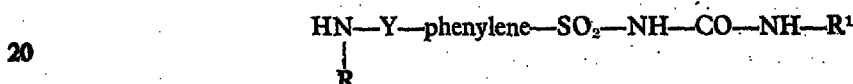
(c) reacting a correspondingly substituted benzenesulphonyl halide with an R¹-substituted urea, or

10 (d) hydrolysing a correspondingly substituted benzenesulphonyl-isourea-ether, benzenesulphonyl-isothiurea-ether or benzenesulphonyl-parabanic acid which may have been obtained by reacting a correspondingly substituted benzenesulphonyl halide with an R¹-substituted isourea-ether, isothiurea-ether or parabanic acid, or

15 (e) replacing the sulphur atom in a correspondingly substituted benzenesulphonyl-thiourea by an oxygen atom by a known method (by which is to be understood herein a method known to be in actual use or described in the relevant literature),

(f) oxidizing a corresponding benzenesulphonyl-urea or benzenesulphenyl-urea, or

(g) introducing the radical ZZ'-X-CO- in one or several reaction stages by acylation into a benzenesulphonyl-urea of the formula



or

25 (h) liberating the hydroxyl group protected by esterification or etherification from a benzenesulphonyl-urea of the aforesaid formula, in which Z represents such a protected hydroxyl group, by catalytic hydrogenation or saponification, and, if desired, converting a resulting free compound into a salt thereof by treatment with an alkaline agent.

Instead of the benzenesulphonyl-isocyanates, there may also be used reaction products of benzenesulphonyl-isocyanates with acid amides such as caprolactam or butyrolactam, or with weakly basic amines such as carbazoles.

30 The benzenesulphonyl-carbamic acid esters or benzenesulphonyl-thiocarbamic acid esters may carry in the alcohol component a low molecular weight alkyl group or a phenyl group. The same applies to the R¹-substituted carbamic acid esters or the corresponding mono-thiocarbamic acid esters.

As carbamic acid halides the chlorides are advantageously used.

35 The benzenesulphonyl-ureas used as starting substances may be unsubstituted at the side of the urea molecule opposite to the sulphonyl group or may be substituted once or twice by alkyl groups or aryl groups. Instead of benzenesulphonyl-ureas substituted in this manner there may be used corresponding N-benzenesulphonyl - N'-acyl - ureas and bis - (benzenesulphonyl) - ureas. (In this case acyl represents an aliphatic acyl group containing up to 4 carbon atoms or a benzyl group). It is possible, for example, to treat such bis - (benzenesulphonyl) - ureas or N - benzenesulphonyl - N' - acyl - ureas with amines of the formula R¹NH₂ and to heat the salts so obtained to elevated temperatures, especially a temperature about 100°C.

45 It is also possible to start from ureas of the formula R¹-NH-CO-NH₂ or from acylated ureas of the formula R¹-NH-CO-NH-acyl, in which acyl represents an aliphatic (preferably of lower molecular weight) or aromatic acid acyl group 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, in which the phenyl groups may be substituted and may be linked with one another directly or by means of a bridge member such as -CH₂-, -NH-, -O- or -S-, or from N:N-di-substituted ureas of the formula R¹-NH-CO-NH-R¹, and to react the said compounds with ZZ'-X-CO-NR-Y- substituted benzenesulphonamides.

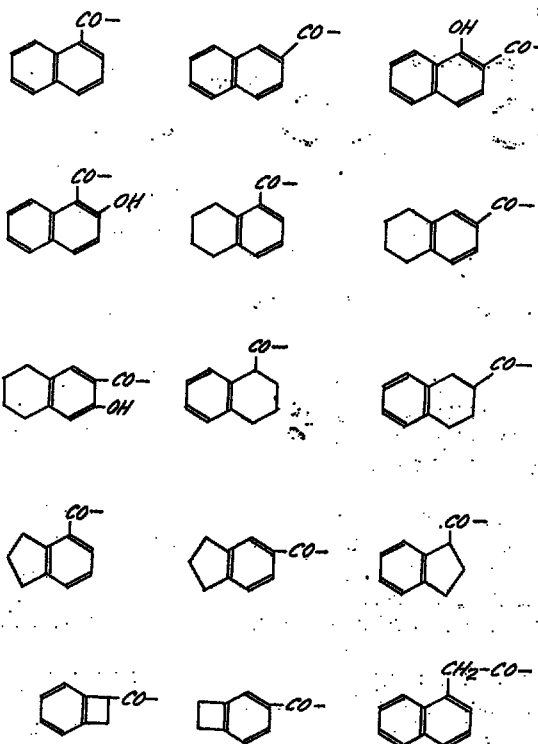
55 In the correspondingly substituted benzenesulphonyl thioureas the sulphur atom can be replaced by an oxygen atom, for example, with the aid of oxides or salts of heavy metals or by the use of oxidizing agents such as hydrogen peroxide, sodium peroxide or nitrous acid. The thioureas can likewise be desulphurized by treatment with phosgene or phosphorus pentachloride. Chloroformic acid amidines or chloroformic acid carbodiimides obtained as intermediates can be converted into the benzene-

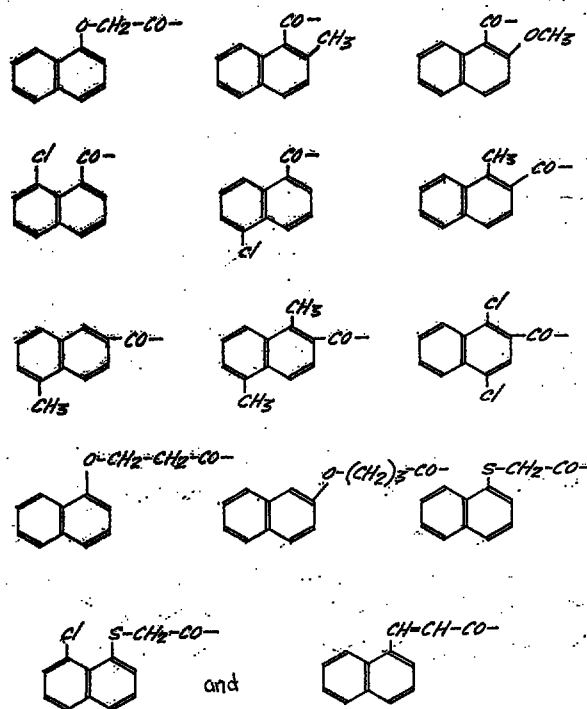
5 sulphonyl-ureas by an appropriate treatment, for example, by hydrolysis or the addition of water.

When the products of the present invention are prepared from intermediates the hydroxyl group of which is benzylated or esterified, the final products obtained can be converted into the new benzenesulphonyl-ureas by a conventional method. The benzyl groups may be split off by catalytic hydrogenation and ester groups may be split off by acid or alkaline hydrolysis.

10 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 can be carried out with the use of solvents, at room temperature or at an elevated temperature.

15 As starting substances there are used, on the one hand, compounds containing a benzene group substituted by the group $ZZ'-X-CO-NR-Y-$. As examples of the component $ZZ'-X-CO-$ of the said group there may be mentioned, for example, the following radicals:





The blood sugar lowering action of the benzenesulphonyl-urea derivatives of the present invention can be ascertained by feeding them to rabbits in a dose of 10 milligrams/kilogram of body weight and determining the blood sugar value according to the known method of Hagedorn-Jensen or by means of an autoanalyzer over a prolonged period of time.

Thus, it has been found, for example, that 10 milligrams/kilogram of body weight of N - [4 - (γ - naphth - (1') - amidopropyl) - benzenesulphonyl] - N' - cyclohexyl-urea provokes after 3 hours a lowering of the blood sugar of 18%, while the hitherto known N - (4 - methyl - benzenesulphonyl) - N' - butyl - urea has no blood sugar lowering properties when fed to rabbits in a dose of less than 25 milligrams/kilogram of body weight.

The strong action of the compounds according to the present invention becomes more evident when the dose is further reduced. When N - [4 - (β - naphth - (1') - amidoethyl) - benzenesulphonyl] - N' - cyclohexyl - urea is administered to rabbits in a dose of 0.3 milligram/kilogram of body weight or N - [4 - (γ - naphth - (1') - amidopropyl) - benzenesulphonyl] - N' - cyclohexyl - urea is administered in a dose of 0.08 milligram/kilogram of body weight, a distinct lowering of the blood sugar level can still be observed.

The present invention further provides pharmaceutical preparations which comprise the compounds of the present invention in admixture or conjunction with a pharmaceutically suitable carrier. The preparations are preferably in the form of orally administerable preparations showing blood sugar lowering action in the treatment of diabetes mellitus. The new compounds used in the preparations can be used in the free form or in the form of their physiologically tolerable salts or in the presence of substances causing such salt formation. For the formation of salts there may be used, for example, alkaline agents 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 products of the invention, the usual adjuvants and carriers, for example talc, starch, lactose, tragacanth or magnesium stearate.

A pharmaceutical preparation containing one of the aforesaid benzenesulphonyl-ureas as 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 about 0.5 to 100 milli-

grams, preferably 2 to 10 milligrams, but considerably 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

- 5 N-[4-(naphth-(1')-amidomethyl)-benzenesulphonyl]-N'-(4-methyl-cyclohexyl)-urea 5
 15 Grams of 4 - (naphth - (1') - amidomethyl) - benzenesulphonamide (melting point 204°C) were dissolved, while stirring, in 130 millilitres of acetone and 22 millilitres of 2N NaOH and, while cooling, (0—5°C) 6.5 grams of 4 - methylcyclohexyl-isocyanate were dropped in. After the termination of the dropwise addition, the temperature was allowed to rise slowly and the reaction mixture was stirred at room temperature for a total of 3 hours. The reaction mixture was filtered with suction, the acetone was removed under reduced pressure in a rotary evaporator at room temperature and the residue was directly crystallized from dimethyl formamide/water. Melting point: 225—226°C.
- 10 In analogous manner there were prepared: 10
- 15 N - [4 - (naphth - (1') - amidomethyl) - benzenesulphonyl] - N' - n - butyl - urea, melting point 142°C from methanol/water; 15
- 20 N - [4 - (naphth - (1') - amidomethyl) - benzenesulphonyl] - N' - cyclohexyl - urea, melting point 198°C from a large amount of ethanol or dimethyl formamide; 20
- 25 from 4 - (β - naphth - (1') - amidoethyl) - benzenesulphonamide (melting point 207°C), 25
- 30 N - [4 - (β - naphth - (1') - amidoethyl) - benzenesulphonyl] - N' - cyclohexyl-urea, melting point 188°C from methanol; 30
- 35 from 4 - (γ - naphth - (1') - amidopropyl) - benzenesulphonamide (melting point 144°C), 35
- 40 N - [4 - (γ - naphth - (1') - amidopropyl) - benzenesulphonyl] - N' - cyclohexyl-urea, melting point 182—184°C from methanol/water; 40
- 45 from 4 - (β - tetralincarb - (2') - amidoethyl) - benzenesulphonamide (melting point 216—218°C), 45
- 50 N - [4 - (β - tetralincarb - (2') - amidoethyl) - benzenesulphonyl] - N' - (4 - methyl-cyclohexyl) - urea, melting point 179—180°C from ethanol/water, and 50
- 55 N - [4 - (β - tetralincarb - (2') - amidoethyl) - benzenesulphonyl] - N' - n - butyl-urea, melting point 180°C from ethanol; 55
- 60 from 4 - (β - indancarb - (5') - amidoethyl) - benzenesulphonamide (melting point 198°C), 60
- 65 N - [4 - (β - indancarb - (5') - amidoethyl) - benzenesulphonyl] - N' - cyclohexyl-urea, melting point 195—196°C from ethanol, 65
- 70 N - [4 - (β - indancarb - (5') - amidoethyl) - benzenesulphonyl] - N' - (4 - methyl-cyclohexyl) - urea, melting point 190—192°C from methanol, and 70
- 75 N - [4 - (β - indancarb - (5') - amidoethyl) - benzenesulphonyl] - N' - n - butyl-urea, melting point 170—171°C from ethanol; 75
- 80 from 4 - (β - indancarb - (5') - amidopropyl) - benzenesulphonamide (melting point 170°C), 80
- 85 N - [4 - (β - indancarb - (5') - amidopropyl) - benzenesulphonyl] - N' - cyclohexyl-urea, melting point 183—184°C from ethanol/water, 85
- 90 N - [4 - (β - indancarb - (5') - amidopropyl) - benzenesulphonyl] - N' - (4 - methyl-cyclohexyl) - urea, melting point 208—210°C from ethanol, and 90
- 95 N - [4 - (β - indancarb - (5') - amidopropyl) - benzenesulphonyl] - N' - n - butyl-urea, melting point 157°C from ethanol/water; 95
- 100 from 4 - (γ - naphthoxy - (1') - acetamidopropyl) - benzenesulphonamide (melting point 196°C), 100
- 105 N - [4 - (γ - naphthoxy - (1') - acetamidopropyl) - benzenesulphonyl] - N' - cyclohexyl - urea, melting point 141°C from ethanol/water; 105
- 110 from 4 - (β - indancarb - (1') - amidoethyl) - benzenesulphonamide (melting point 77°C), 110
- 115 N - [4 - (β - indancarb - (1') - amidoethyl) - benzenesulphonyl] - N' - cyclohexyl-urea, melting point 159°C from methanol/water; 115
- 120 from 4 - (β - 3' - hydroxytetralincarb - (2') - amidopropyl) - benzenesulphonamide (melting point 184—185°C), 120
- 125 N - [4 - (β - 3' - hydroxytetralincarb - (2') - amidopropyl) - benzenesulphonyl] - N' - cyclohexyl - urea, melting point 162—163°C from ethanol/water; 125
- 130 from 4 - (δ - naphth - (1') - amidobutyl) - benzenesulphonamide (melting point 161°C), 130
- 135 N - [4 - (δ - naphth - (1') - amidobutyl) - benzenesulphonyl] - N' - cyclohexyl-urea, melting point 185°C from ethanol/water; 135

- from 4 - (β - 3' - chloronaphth - (2') - amidoethyl) - benzenesulphonamide (melting point 224°C),
 N - [4 - (β - 3' - chloronaphth - (2') - amidoethyl) - benzenesulphonyl] - N' - cyclohexyl - urea, melting point 206°C from ethanol/water; and
 5 from 4 - (β - 3' - methoxynaphth - (2') - amidoethyl) - benzenesulphonamide (melting point 167°C),
 N - [4 - (β - 3' - methoxynaphth - (2') - amidoethyl) - benzenesulphonyl] - N' - cyclohexyl - urea, melting point 187°C from ethanol/water. 5

EXAMPLE 2

- 10 N-[4-(γ -naphth-(2')-amidopropyl)-benzenesulphonyl]-N'-cyclohexyl-urea 10
 5 Grams of cyclohexylamine were added, while stirring, to 22 grams of N-[4-(γ -naphth-(2')-amidopropyl)-benzenesulphonyl]-ethyl-urethane (melting point 263°C) in 120 millilitres of toluene. The temperature was raised to 130°C, whereby the reaction set in with the accompanying release of methanol. The reaction
 15 mixture was cooled after about 30 minutes, and the precipitated urea was filtered off 15
 with suction and recrystallized from ethanol. It had a melting point of 190°C.

EXAMPLE 3

- N-[4-(β -tetralincarb-(2')-amidoethyl)-benzenesulphonyl]-N'-cyclohexyl-urea
 2.7 Grams of N - [4 - (β - tetralincarb - (2') - amidoethyl) - benzenesulphonyl] -
 20 N' - cyclohexyl - isourea methyl ether (prepared by reacting N - [4 - (β - tetralin- 20
 carb - (2') - amidoethyl) - benzenesulphonyl] - N' - cyclohexyl - thiourea with
 mercury oxide in methanol), melting point 114—155°C, and 30 millilitres of concentrated hydrochloric acid were heated for 5 minutes on a steam bath. The precipitate
 which solidified on cooling was recrystallized from ethanol, melting point 190°C.
 25 The mixed melting point with the substance prepared by a different method (Example 25
 4) showed no depression.

EXAMPLE 4

- N-[4-(β -tetralincarb-(2')-amidoethyl)-benzenesulphonyl]-N'-cyclohexyl-urea
 5.0 Grams of N - [4 - (β - tetralincarb - (2') - amidoethyl) - benzenesulphonyl] -
 30 N' - cyclohexyl - thiourea (prepared by reacting 4 - (β - tetralincarb - (2') - amido- 30
 ethyl) - benzenesulphonamide with cyclohexyl-mustard oil in the presence of potassium carbonate, acetone and dimethyl formamide), melting point 137—139°C after recrystallization from acetic ester/petroleum ether, were dissolved in an excess of 1N NaOH, and hydrogen peroxide of 3% strength was added. The mixture was heated
 35 for a short time on a steam bath, it was allowed to cool, filtered and the filtrate was 35
 acidified. The precipitated sulphonyl-urea was recrystallized from ethanol. It had a melting point of 190°C.

EXAMPLE 5

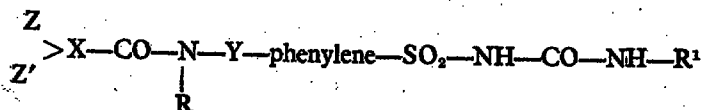
- N-[4-(γ -naphthyl-(1')-acetamidopropyl)-benzenesulphonyl]-N'(4-methyl-cyclohexyl)-
 urea 40
 16.8 Grams of 4 - (γ - naphthyl - (1') - acetamidopropyl) - benzene - sulphon-
 amide sodium (melting point of the free sulphonamide 173—174°C) and 22 grams of
 N:N - diphenyl - N' - (4 - methyl - cyclohexyl) - urea in 40 millilitres of dimethyl
 formamide were maintained for 7 hours at 100°C. The reaction mixture was cooled,
 45 water was added and the mixture was rendered alkaline by means of 2N NaOH. 45
 The diphenylamine formed was extracted with ether, and the aqueous phase was treated
 with charcoal and acidified. The precipitate was extracted with NH₄OH of 1%
 strength, acidified and recrystallized from ethanol/water. The product obtained had
 a melting point of 167—168°C.

EXAMPLE 6

- N-[4-(β -indancarb-(2')-amidoethyl)-benzenesulphonyl]-N'-cyclohexyl-urea 50
 12 Grams of N - [4 - (β - indancarb (2') - amidoethyl) - benzenesulphonyl] -
 urea (melting point 201—202°C), 350 millilitres of toluene, 2.15 grams of glacial
 acetic acid and 3.7 grams of cyclohexylamine were stirred for 3 hours at 120°C.
 55 The reaction mixture was concentrated under reduced pressure and the residue was 55
 treated with ammonia of 1% strength, the extract was acidified and the reaction
 product was recrystallized from methanol. It had a melting point of 195—196°C.

WHAT WE CLAIM IS:—

1. A benzenesulphonyl-urea of the general formula



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

X represents an aromatic bicyclic hydrocarbon group which may be partially hydrogenated in one ring, and which may be linked to the adjacent carbonyl group by a lower alkylene, lower O-alkylene, lower S-alkylene or $-\text{CH}=\text{CH}-$ group,

Z represents a hydrogen or halogen atom, or a lower alkyl, lower alkoxy or hydroxyl group,

Z' represents a hydrogen or halogen atom, or a lower alkyl or lower alkoxy group,

Y represents a straight chain or branched hydrocarbon group containing 1 to 4 carbon atoms,

R represents a hydrogen atom, a lower alkyl group, or a phenyl-lower alkyl group, and

R¹ represents

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

(b) an alkoxyalkyl, alkylmercaptoalkyl or alkylsulphinylalkyl group containing 4 to 8 carbon atoms of which at least 2 belong to the alkylene part of the alkoxyalkyl, alkylmercaptoalkyl or alkylsulphinylalkyl group,

(c) a phenyl-lower alkyl group or phenylcyclopropyl group,

(d) a cyclohexyl-lower alkyl, cycloheptylmethyl, cycloheptylethyl or cyclooctyl-methyl group,

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

(f) a lower alkyl-cycloalkyl group containing 5 to 8 ring carbon atoms or a lower alkoxy-cyclohexyl group,

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

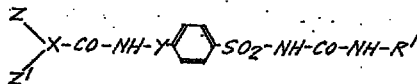
(h) a cyclohexenyl or cyclohexenylmethyl group,

(i) a heterocyclic ring containing 4 or 5 carbon atoms and 1 oxygen atom or 1 sulphur atom and which may also contain up to 2 ethylenic double bonds, or

(k) a heterocyclic ring linked to the adjacent nitrogen atom by means of a methylene group containing 4 or 5 carbon atoms, 1 oxygen atom or 1 sulphur atom and which may also contain up to 2 ethylenic double bonds.

2. A physiologically tolerable salt of a benzenesulphonyl-urea as claimed in claim 1.

3. A benzenesulphonyl-urea of the general formula



in which

Z represents a hydrogen or halogen atom, or a lower alkyl, lower alkoxy or hydroxyl group,

Z' represents a hydrogen or halogen atom, or a lower alkyl or lower alkoxy group,

X represents an aromatic bicyclic hydrocarbon group which may be partially hydrogenated in one ring, and which is linked to the adjacent carbonyl group by a single chemical bond or by a $-\text{CH}_2-\text{CH}_2-$ or $-\text{O}-\text{CH}_2-$ group,

Y represents a straight chain or branched hydrocarbon group containing 1 to 3 carbon atoms, and

R¹ represents

(a) an alkyl group containing 3 to 6 carbon atoms,

(b) a cycloalkyl group containing 5 to 8 carbon atoms,

(c) a 4-methyl-cyclohexyl group,

(d) a cyclohexenyl group,

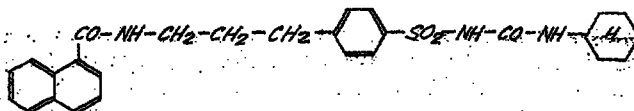


(e) an endomethylene-cyclohexyl-methyl or endomethylene-cyclohexenyl-methyl group, or

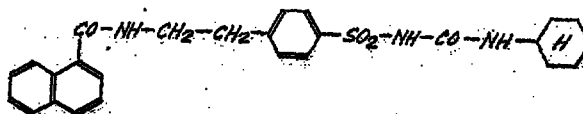
(f) a cyclohexyl-methyl group.

4. A physiologically tolerable salt of a benzenesulphonyl-urea as claimed in claim

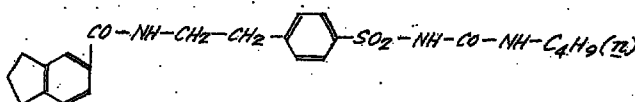
5. N - [4 - (γ - naphth - (1') - amidopropyl) - benzenesulphonyl] - N' - cyclohexyl - urea of the formula



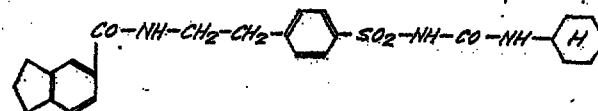
6. N - [4 - (β - naphth - (1') - amidoethyl) - benzenesulphonyl] - N' - cyclohexyl - urea of the formula



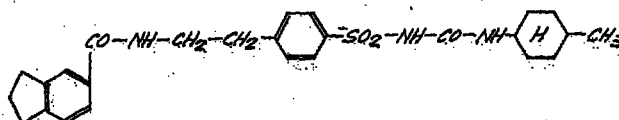
7. N - [4 - (β - indancarb - (5') - amidoethyl) - benzenesulphonyl] - N' - n-butyl - urea of the formula



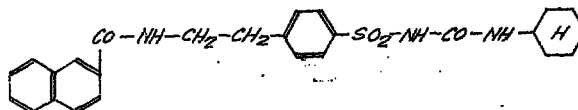
8. N - [4 - (β - indancarb - (5') - amidoethyl) - benzenesulphonyl] - N' - cyclohexyl - urea of the formula



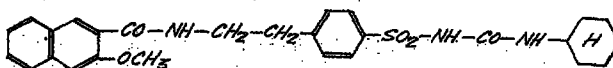
9. N - [4 - (β - indancarb - (5') - amidoethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea of the formula



10. N - [4 - (β - tetralincarb - (2') - amidoethyl) - benzenesulphonyl] - N' - cyclohexyl - urea of the formula



11. N - [4 - (β - 3' - methoxynaphth - (2') - amidoethyl) - benzenesulphonyl] - N' - cyclohexyl - urea of the formula



12. A physiologically tolerable salt of the compound claimed in any one of claims 5 to 11.

13. Any one of the benzenesulphonyl-ureas as claimed in claim 1 and described in the Examples herein.

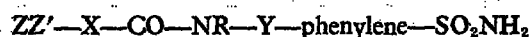
14. A process for the manufacture of a benzenesulphonyl-urea as claimed in claim 1, or a salt thereof, which comprises

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



with an R¹-substituted amine or a salt thereof, protecting any hydroxyl group represented by Z during the reaction by benzylation or esterification and liberating such a protected group after the reaction by catalytic hydrogenation or saponification,

- or
(b) reacting a benzenesulphonamide of the formula



or a salt thereof with an R¹-substituted isocyanate, carbamic acid ester, thio-carbamic acid ester, carbamic acid halide or urea,

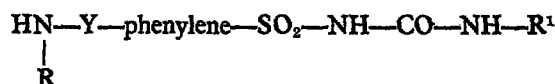
- or
(c) reacting a correspondingly substituted benzenesulphonyl halide with an R¹-substituted urea,

- or
(d) hydrolysing a correspondingly substituted benzenesulphonyl-isourea-ether, benzenesulphonyl-isothiurea-ether or benzenesulphonyl-parabanic acid which may have been obtained by reacting a correspondingly substituted benzenesulphonyl halide with an R¹-substituted isourea-ether, isothiurea-ether or parabanic acid,

- or
(e) replacing the sulphur atom in a correspondingly substituted benzenesulphonyl-thiurea by an oxygen atom by a known method (as hereinbefore defined),

- or
(f) oxidizing a corresponding benzenesulphinyl-urea or benzenesulphenyl-urea,

- or
(g) introducing the radical ZZ'-X-CO- in one or several reaction stages by acylation into a benzenesulphonyl-urea of the formula



- or
(h) liberating the hydroxyl group protected by esterification or etherification from a benzenesulphonyl-urea of the formula given in claim 1, in which Z represents such a protected group, by catalytic hydrogenation or saponification,

and, if desired, converting a resulting free compound into a salt thereof by treatment with an alkaline agent.

15. A process for the manufacture of a benzenesulphonyl-urea as claimed in claim 1 or a salt thereof, conducted substantially as described herein.

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

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

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

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

20. A pharmaceutical preparation which comprises the compound claimed in any one of claims 5 to 11, in admixture or conjunction with a pharmaceutically suitable carrier.

21. A pharmaceutical preparation which comprises a physiologically tolerable salt as claimed in claim 13, in admixture or conjunction with a pharmaceutically suitable carrier.

22. A pharmaceutical preparation as claimed in any one of claims 16 to 21, which is in a form suitable for oral administration.

23. A pharmaceutical preparation as claimed in any one of claims 16 to 22, which is in unit dosage form.

24. A pharmaceutical preparation as claimed in claim 23, wherein each unit dose contains 0.5 to 100 milligrams of the active ingredient.



25. A pharmaceutical preparation as claimed in claim 23, wherein each unit dose contains 2 to 10 milligrams of the active ingredient.

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1968.
Published by the Patent Office, 25 Southampton Buildings, London, W.C.2, from which
copies may be obtained.



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