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PATENT SPECIFICATION

NO DRAWINGS

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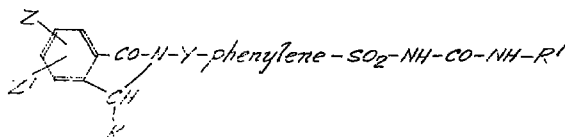
COMPLETE SPECIFICATION

Benzenesulphonyl-Ureas and process for preparing them

We, FARBWERKE HOECHST AKTIENGESSELLSCHAFT, vormals Meister Lucius and 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.

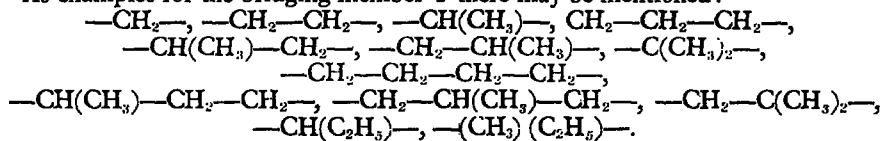
The present invention provides benzenesulphonyl-ureas of the general formula I



- 10 and the physiologically tolerable salts thereof, which benzenesulphonyl-ureas, in the free form or in the form of their physiologically tolerable salts, possess blood sugar lowering properties and are distinguished by a strong and particularly long lasting lowering action on the blood sugar level. 10
- 15 In the above formula
R represents a hydrogen atom or a methyl group, 15
Z and Z' which may be the same or different each represents a hydrogen atom, a lower alkyl group, a lower alkoxy group or a halogen atom,
Y represents a straight-chain or branched hydrocarbon group containing 1 to 4 carbon atoms, and
20 R' represents 20
(a) an alkyl group containing 3 or 4 carbon atoms
(b) a cyclohexyl-methyl group,
(c) an endoalkylene - cyclohexyl, endoalkylene - cyclohexenyl, endoalkylene-cyclohexyl - methyl or endoalkylene - cyclohexenyl - methyl group, each containing 1 or 2 endoalkylene carbon atoms, 25
(d) a lower alkyl - cyclohexyl group,
(e) a lower - cyclohexyl group,
(f) a cycloalkyl group containing 5 to 8 carbon atoms, or
(g) a cyclohexenyl or cyclohexenyl-methyl group.
30 In the above and the following definitions in this Specification "lower alkyl" or "lower alkoxy" groups always mean alkyl or alkoxy groups containing 1 to 4 carbon atoms in a straight or branched chain. "Lower acyl" represents an acyl group (organic acid group) containing up to 4 carbon atoms, preferably a straight-chain or branched alkanoyl group of the chain length indicated. 30
35 R' may represent, for example, propyl, isopropyl, butyl, isobutyl or sec. butyl. 35
Within the scope of the present invention there are particularly preferred compounds containing as R' cycloaliphatic hydrocarbon group as defined in paragraphs (b)

to (g) above. Said groups comprise, for example, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, methylcyclohexyl, ethyl - cyclohexyl, propyl - cyclohexyl, isopropyl - cyclohexyl, methoxy - cyclohexyl, ethoxy - cyclohexyl, propoxy - cyclohexyl or isopropoxy - cyclohexyl. The alkyl groups or the alkoxy groups can be present in the 2-, 3- or preferably 4-position, in the cis- as well as in the trans-position. Furthermore, there may be mentioned: cyclohexyl - methyl, endomethylene - cyclohexyl (2,2,1 - tricycloheptyl), endoethylene - cyclohexyl (2,2,2 - tricyclooctyl), endomethylene - cyclohexenyl, endoethylene - cyclohexenyl, endomethylene - cyclohexyl - methyl, endoethylene, endo-hexyl - methyl, endomethylene - cyclohexenyl - methyl or endoethylene - cyclohexenyl-methyl in the cis as well as in the trans form.

As examples for the bridging member Y there may be mentioned:

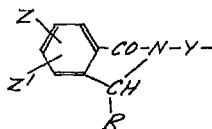


As examples of the substituents represented by Z and Z' there may be mentioned: Methyl, ethyl, n - propyl, isopropyl, n - butyl, isobutyl, sec. butyl or tert. butyl as well as the corresponding alkoxy groups, fluorine, chlorine, bromine or iodine. If halogen atoms are present, they are preferably chlorine atoms.

The phenylene group indicated in the general formula by -phenylene- is preferably unsubstituted, but it can also be substituted once or several times by halogen, lower alkyl or lower alkoxy. It can contain the remaining parts of the molecule in ortho, meta or para-position to one another, the para-position being preferred.

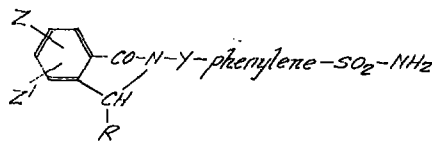
The present invention furthermore provides a process for the manufacture of the above-specified benzenesulphonyl ureas and of their salts. These benzenesulphonyl-ureas can be prepared according to the following methods:

a) Benzenesulphonyl isocyanates, benzenesulphonyl carbamic acid esters, benzenesulphonyl thiocarbamic acid esters, benzenesulphonyl carbamic acid halides or benzenesulphonyl-ureas which are substituted by the group



are reacted with R¹ - substituted amines or, if desired, with their salts.

b) Benzenesulphonamides of the formula



II

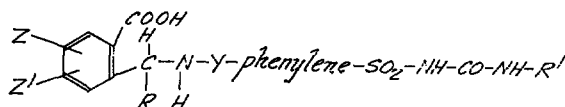
or, if desired, their salts, are reacted with R¹-substituted isocyanates, carbamic acid esters, thiocarbamic acid esters, carbamic acid halides or ureas.

c) Correspondingly substituted benzenesulphonyl - isourea ethers, benzenesulphonyl - isothiurea ethers or benzenesulphonyl - parabanic acids are hydrolysed.

d) The sulphur atom in correspondingly substituted benzenesulphonyl - thioureas is replaced by an oxygen atom by a known method (which it is to be understood herein in a method known to be in actual use or described in the relevant literature).

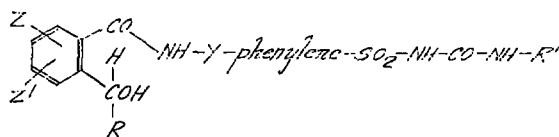
e) Corresponding benzenesulphenyl - ureas or benzenesulphenyl - ureas are oxidized.

f) In benzenesulphonyl - ureas of the formula



III

or



IV

the phthalimidino ring is formed by a known method, and this formation can also take place in several stages, if desired via the functional derivatives of the group —COOH— or —CH—OH .



The products obtained according to the afore-mentioned methods can be treated with alkaline agents if salt formation is desired.

According to the nature of the starting materials and the working conditions the phthalimidino ring can be opened unintentionally if the process is carried out according to methods (a) to (e). In such cases the method in question must be followed by the method described under paragraph (f) in order to close the ring again.

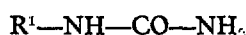
Instead of benzenesulphonyl isocyanates there can also be used the reaction products of benzenesulphonyl isocyanates with acid amides, such as caprolactam or butyrolactam, and furthermore with weakly basic amines, for example carbazoles.

The above-mentioned benzenesulphonyl - carbamic acid esters or benzenesulphonyl - thiocarbamic acid esters can contain a low molecular weight alkyl group or a phenyl group in the alcohol component. The same applies to the R^1 -substituted carbamic acid esters or the corresponding mono-thiocarbamic acid esters. By a low molecular weight or lower alkyl group there is always to be understood herein an alkyl radical group containing at most 4 carbon atoms.

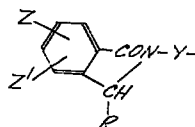
As carbamic acid halides, the chlorides are particularly suitable.

The benzenesulphonyl-ureas to be used as starting materials in the process of the present invention may be unsubstituted at the side of the urea molecule opposite the sulphonyl group or they may be mono- or di-substituted by preferably lower alkyl or aryl groups. Instead of benzenesulphonyl-ureas substituted in such a manner, there may also be used corresponding N - benzenesulphonyl - N' - acyl - ureas and bis - (benzenesulphonyl) - ureas. Such bis - (benzenesulphonyl) - ureas or N - benzenesulphonyl - N' - acyl - ureas may, for example, be treated with amines $\text{R}^1\text{—NH}_2$ and the salts obtained may be then heated to elevated temperatures, in particular to temperatures above 100°C .

Furthermore, it is possible to start from ureas of the formula



or from acylated ureas of the formula $\text{R}^1\text{—NH—CO—NH—acyl}$, in which acyl represents a preferably low molecular weight aliphatic or an aromatic acid group or a nitro group, or from phenyl-ureas of the formula $\text{R}^1\text{—NH—CO—NH—C}_6\text{H}_5$, or from diphenyl-ureas of the formula $\text{R}^1\text{—NH—CO—N(C}_6\text{H}_5)_2$, in which the phenyl groups may be substituted and/or linked with one another either directly through a bridging member such as $\text{—CH}_2\text{—}$, —NH— , —O— or —S— , or from N,N - disubstituted ureas of the formula $\text{R}^1\text{—NH—CO—NH—R}^1$ and to react these ureas with benzenesulphonamides substituted by the grouping



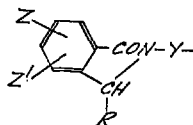
The replacement of the sulphur atom in the correspondingly substituted benzenesulphonyl - thioureas by an oxygen atom can be carried out, for example, with the aid of oxides or salts of heavy metals or even by the use of oxidizing agents such as hydrogen peroxide, sodium peroxide or nitrous acid.

The thioureas can also be desulphurized by a treatment by means of phosgene or phosphorus pentachloride. Chloroformic acid amidines or carbodiimides, obtained as intermediates, can be converted into benzenesulphonyl ureas by appropriate measures, for example by saponification or the addition of water.

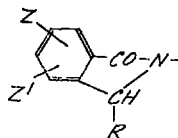
The formation of the phthalimidino compound—starting from a compound of the formula III or IV—can likewise be effected by heating said compound to elevated temperatures.

As regards the reaction conditions, the forms of carrying out the process of the present invention may in general vary within wide limits and may be adapted to each individual case. For example, the reactions using solvents may be carried out at room temperature or at an elevated temperature.

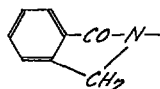
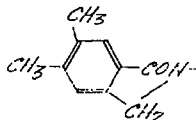
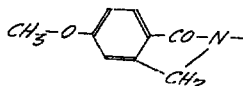
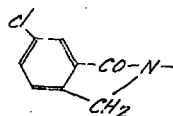
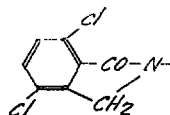
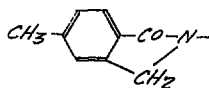
As starting materials, there are used on the one hand compounds which contain a benzene group substituted by the group



As examples of the component



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



The blood sugar lowering action of the benzenesulphonyl urea derivatives described above was determined by measuring over a prolonged period of time, according to the known method of Hagedorn-Jensen or with an autoanalyzer the blood sugar level of rabbits which had been fed with the compounds in doses of 10 milligrams/kilogram of body weight.

Thus, it was found, for example, that 10 milligrams/kilograms of body weight of N - [4 - (β - phthalimidino - α - methyl - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea provoked, after 3 hours, a lowering of the blood sugar level by 14%, whereas the hitherto known N - (4 - methyl - benzenesulphonyl) - N' - butyl - urea, administered to rabbits in a dose of less than 25 milligrams/kilogram of body weight, provoked no lowering of the blood sugar level.

The strong blood sugar lowering action of the compounds of the present invention becomes particularly evident when reduced doses are administered. When N - [4 - (β - phthalimidino - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea is administered to rabbits in a dose of 2 milligrams/kilogram of body weight, a distinct lowering of the blood sugar level (- 17%) can still be detected.

The compounds of the present invention are intended to be used preferably for the manufacture of pharmaceutical preparations that have a blood sugar lowering action in the treatment of diabetes mellitus; they can be used as such or in the form of their physiologically tolerable salts or in the presence of substances that cause the formation of such salts. For such salt formation, there can be used, for example, alkaline agents such as alkali metal hydroxides, alkaline earth metal hydroxides, alkali metal carbonates and alkaline earth metal carbonates, alkali metal bicarbonates and alkaline earth metal bicarbonates.

Accordingly, the present invention also provides pharmaceutical preparations which comprise the new benzenesulphonyl ureas or their physiologically tolerable salts, in admixture or conjunction with a pharmaceutically suitable carrier. The preparations are preferably in a form suitable for oral administration.

As pharmaceutical preparations there enter into consideration preferably tablets which contain, in addition to the compounds of the invention, the usual adjuvants and carriers such as talc, starch, lactose, tragacanth or magnesium stearate.

A preparation containing the above - mentioned benzenesulphonyl ureas as the active substance, for example a tablet or a powder, with or without the above-mentioned additives, is preferably processed into a suitable unit dosage form. The dose chosen should comply with the efficacy of the benzenesulphonyl - urea used and with the desired effect. Advantageously, the dosage per unit is in the range of from about 0.5 to 100 mg, preferably 2 to 10 mg. However, considerably higher or low dosage units may also be used which, if desired, may be divided to multiplied prior to their application.

The following Examples illustrate the invention.

EXAMPLE 1:

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

a) 53.6 grams of phthalide are dissolved in 500 cc of xylene. 88.8 grams of 4 - (β - aminoethyl) - benzenesulphonamide sodium are added while stirring. The mixture is heated for 30 minutes at the boil, and 24 grams of glacial acetic acid are added dropwise. From this mixture the xylene is removed by distillation. The residue obtained is dissolved in 1N - sodium hydroxide solution, and the solution is clarified with charcoal and acidified after filtration. A precipitate of 4 - (β - o - hydroxymethyl - benzamido - ethyl) - benzenesulphonamide is obtained in a good yield, and this precipitate is filtered with suction, washed with water and dried. The substance melts at 163—165° C.

b) By heating the reaction mixture for 90 minutes at about 200°C, cooling and recrystallizing it from methanol, 4 - (β - phthalimidino - ethyl) - benzenesulphonamide melting at 251—253°C is obtained in a good yield from the substance prepared according to the method described under paragraph (a).

c) 15 grams of the sulphonamide obtained according to paragraph (b) are suspended in 250 cc of acetone. The suspension is stirred, 13 grams of dry, ground potassium carbonate are added, and the whole is heated at the boil for 1 hour. On continuing stirring and heating, 6.3 grams of cyclohexyl isocyanate are added dropwise. After boiling for 6 hours the reaction is terminated, the solvent is distilled off under reduced pressure, and the residue is taken up in water, filtered after treatment with charcoal and acidified. A precipitate of N - [4 - (β - phthalimidino - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea is obtained in a good yield. The substance melts at 213—215° C after recrystallization from methanol.

EXAMPLE 2:

N - [4 - (β - phthalimidino - α - methyl - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea

a) 20 grams of 4 - (β - phthalimido - α - methyl - ethyl) - benzenesulphonamide, obtained from phthalic acid anhydride and 4 - (α - methyl - β - aminoethyl) - benzene-sulphonamide, are dissolved in 280 cc of ethanol. 210 cc of concentrated hydrochloric acid and 42 grams of granulated tin are added. After heating the mixture at the boil for 3 hours, it is diluted with water. The precipitate of 4 - (β - phthalimidino - α - methyl - ethyl) - benzenesulphonamide formed is filtered with suction, and the substance is washed with water and dried. Melting point 244—247°C.

b) 11 grams of the sulphonamide obtained according to paragraph (a) are suspended in 250 cc of acetone, 8.7 grams of potassium carbonate are added, and the whole is heated at the boil under reflux for 1 hour. After the addition of 4 grams of cyclohexyl isocyanate the mixture is kept for 5½ hours at the boiling temperature while stirring simultaneously. The acetone is then distilled off, and the residue is dissolved in water. The solution is clarified with charcoal, and the filtrate is acidified. A crystalline precipitate of N - [4 - (β - phthalimidino - α - methyl - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea is obtained in a good yield. It is filtered with suction and recrystallized from methanol. The substance melts at 198—200°C.

In an analogous manner there is obtained from 4 - (β - phthalimidino - α - methyl - ethyl) - benzenesulphonamide and butyl - isocyanate, N - [4 - (β - phthalimidino - α - methyl - ethyl) - benzenesulphonyl] - N' - butyl - urea which melts at 166—168°C (from methanol).

EXAMPLE 3:

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

a) 27 grams of phthalide are dissolved in 200 cc of xylene. 44.4 grams of 4 - (β - aminoethyl) - benzenesulphonamide sodium are added while stirring. The solution is heated at the boil for 30 minutes, 12 grams of glacial acetic acid are added dropwise and stirring is continued for a further 90 minutes at the boiling temperature. The residue, obtained after having removed the solvent under reduced pressure, is dissolved in 1N-sodium hydroxide solution. It is filtered with the use of charcoal, and the filtrate is acidified. A crystalline precipitate of 4 - (β - o - hydroxymethyl - benzamido - ethyl) - benzenesulphonamide is obtained which is filtered with suction, washed with water and dried. The substance melts at 161—163°C.

b) 6.7 grams of the sulphonamide obtained according to paragraph (a) are dissolved in 10 cc of 2N - sodium hydroxide solution. After the addition of 50 cc of acetone, the solution is cooled to about 0°C, and 2.5 grams of cyclohexyl isocyanate are added while stirring. The mixture is then stirred for 2 hours at room temperature and diluted with water. It is filtered, and the filtrate is acidified. A crystalline precipitate is obtained which is filtered with suction, washed with water and recrystallized from methanol/dimethylformamide. The N - [4 - (β - phthalimidino - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea thus obtained melts at 213—215°C and shows no depression of the melting point with the substance obtained according to Example 1.

EXAMPLE 4:

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

a) 4.57 grams of N - [4 - (β - phthalimidino - ethyl) - benzenesulphonyl] - N' - cyclohexyl - thiourea are dissolved in 250 cc of methanol. A suspension of 2.2 grams of mercury oxide in 50 cc of methanol is added while stirring, and the whole is heated for 3½ hours at about 60°C while continuing the stirring. After cooling, the solution is filtered and concentrated. The concentrated methanolic solution obtained is carefully mixed with water, and a crystalline precipitate of N - [4 - (β - phthalimidino - ethyl) - benzenesulphonyl] - N' - cyclohexyl - isourea methyl ether is obtained. The substance melts at 139—141°C after recrystallization from methanol.

b) 0.4 gram of the isourea methyl ether obtained according to paragraph (a) are heated for 5 minutes on a steam bath with 10 cc of concentrated hydrochloric acid. The mass is then cooled, and the crystals obtained are filtered with suction and washed with water. After recrystallization from methanol, N - [4 - (β - phthalimidino-ethyl) - benzenesulphonyl] - N' - cyclohexyl urea is obtained in a good yield. The substance melts at 213—215°C.

EXAMPLE 5:

N - [4 - (β - phthalimidino - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea
4.2 grams of N - [4 - (β - phthalimidino - ethyl) - benzenesulphonyl] - carbamic acid methyl ester (obtained by reacting 4 - (β - phthalimidino - ethyl) - benzenesulph-

5 onamide and chloroformic acid methyl ester in acetone in the presence of potassium carbonate, melting point 228—231°C) are suspended in 150 cc of dioxan. After the addition of 1.1 grams of cyclohexyl amine the suspension is heated at the boil under reflux for 90 minutes. The solvent is then removed under reduced pressure, and the residue obtained is recrystallized from methanol. In order to purify the reaction product it is taken up in dilute aqueous ammonia and filtered, and the filtrate is acidified. The precipitate of N - [4 - (β - phthalimidino - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea thus obtained melts at 213—215°C after recrystallization from methanol. 5

EXAMPLE 6:

10 N - [4 - (β - phthalimidino - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea
 a) 21.6 grams of 4 - (β - phthalimidino - ethyl) - benzenesulphonamide are dissolved in 200 cc of ethanol. A solution of 11.4 grams of potassium cyanate in 15 cc of water is added while shaking. The solution is heated at the boil under reflux on a steam bath, and the solvent alcohol is then distilled off to a large extent. The residue obtained is dissolved in water. The solution is filtered and acidified. The precipitate, thus 15
 obtained, is taken up in dilute ammonia of about 1% strength. After acidification there is obtained a crystalline mass of N - [4 - (β - phthalimidino - ethyl) - benzenesulphonyl] - urea. The substance melts at 220—222°C after recrystallization from a mixture of methanol/dimethylformamide with decomposition.
 20 b) 3.6 grams of the urea obtained according to paragraph (a) are suspended in 100 cc of toluene. After the addition of 0.66 gram of glacial acetic acid and 1.1 gram of cyclohexylamine the suspension is heated at the boil under reflux on an oil bath for 3½ hours. The reaction mixture is cooled and allowed to stand overnight. On the next morning the crystallized precipitate is filtered with suction, washed with diisopropyl ether and water and recrystallized from a mixture of methanol/dimethylformamide. 25
 The N - [4 - (β - phthalimidino - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea obtained in a good yield melts at 213—215°C.

EXAMPLE 7:

30 N - [4 - (β - 5 - chlorophthalimidino - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea
 11.7 grams of 4 - (β - 5 - chlorophthalimidino - ethyl) - benzenesulphonamide (prepared by reduction of the corresponding phthalimide derivative, melting point 176—178°C) and 9.2 grams of potassium carbonate are heated at the boil in 150 cc of acetone for 1 hour while stirring. 4.2 grams of cyclohexyl isocyanate are then added dropwise, and stirring and heating are continued for 4 hours. After concentration under reduced pressure, the residue obtained is mixed with dilute hydrochloric acid and the crystalline mass formed is filtered with suction. The substance is dissolved in ammonia of about 1% strength, and the filtrate is acidified with dilute hydrochloric acid. The N - [4 - (β - 5 - chloro - phthalimidino - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea is obtained in a good yield. The substance melts at 151—153°C after recrystallization from isopropanol. 40

In an analogous manner there is obtained from the same benzenesulphonamide and 4 - methyl - cyclohexyl isocyanate, N - [4 - (β - 5 - chlorophthalimidino - ethyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea melting at 134—136°C after recrystallization from methanol, and with the use of n - butyl isocyanate, N - [4 - (β - 5 - chlorophthalimidino - ethyl) - benzenesulphonyl] - N' - butyl - urea. The substance melts at 150—162°C after recrystallization from isopropanol. 45

EXAMPLE 8:

50 N - [4 - (phthalimidino - methyl) - benzenesulphonyl] - N' - cyclohexyl - urea
 15 grams of 4 - (phthalimidino - methyl) - benzenesulphonamide (obtained from phthalimidino - methyl - benzene by chlorosulphonation and reaction of the sulphonic acid chloride, obtained as intermediate product, with ammonia, melting point 228—230°C, or from 4 - phthalimidino - methyl - benzenesulphonamide by reduction with granulated tin and concentrated hydrochloric acid in ethanol) are boiled under reflux in 250 cc of acetone in the presence of 13.8 grams of potassium carbonate while stirring simultaneously. 6.3 grams of cyclohexyl isocyanate are then added dropwise at the boiling temperature of the acetone and stirring and boiling are continued for a further 6 hours. After standing over night, the reaction mixture is filtered with suction, and the salt mixture obtained is dissolved in water. The solution is filtered. 55
 After acidification, a crystalline precipitate of N - [4 - (phthalimidino - methyl) - benzenesulphonyl] - N' - cyclohexyl urea is obtained in a good yield. It melts at 203— 60

205°C after recrystallization from methanol.

In an analogous manner there is obtained from 4 - (phthalimidino - methyl) - benzenesulphonamide and 4 - methyl - cyclohexyl isocyanate, N - [4 - (phthalimidino - methyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea melting at 191—193°C (from methanol).

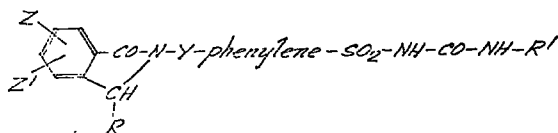
EXAMPLE 9:

N - [4 - (β - 3 - ethyl - phthalimidino - ethyl) - benzenesulphonyl] - N' - cyclohexyl-urea

7.6 grams of 4 - (β - 3 - ethyl - phthalimidino - ethyl) - benzenesulphonamide (melting point 215—217°C—prepared from 2 - β - phenylethyl - 3 - ethyl - phthalimidine by sulphochlorination and reaction with ammonia) and 6.2 grams of potassium carbonate are added to 100 cc of acetone. The mixture is heated at the boil under reflux for 1 hour while stirring. 2.8 grams of cyclohexyl isocyanate are then added dropwise, and stirring is continued for a further 3 hours at the boiling temperature. The reaction product is dissolved in water, the solution is filtered and the filtrate is acidified with dilute hydrochloric acid. The crystalline precipitate thus obtained is filtered with suction and dissolved in ammonia of 1% strength. Upon acidification with acetic acid, N - [4 - (β - ethyl - phthalimidino - ethyl) - benzenesulphonyl] - N' - cyclohexyl urea is obtained in good yield. It melts at 105—107°C.

WHAT WE CLAIM IS:—

1. A compound of the formula



in which

R represents a hydrogen atom or a methyl group,

R¹ represents

(a) an alkyl group containing 3 or 4 carbon atoms,

(b) a cyclohexyl-methyl group

(c) an endoalkylene - cyclohexyl, endoalkylene - cyclohexenyl, endoalkylene - cyclohexyl - methyl or endoalkylene - cyclohexenyl - methyl group, each containing 1 or 2 endoalkylene carbon atoms,

(d) a lower alkyl - cyclohexyl group,

(e) a lower alkoxy - cyclohexyl group,

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

(g) a cyclohexenyl or cyclohexenyl-methyl group,

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

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

2. A compound of the formula given in claim 1 in which

Z represents a hydrogen atom or a methyl group,

R¹ represents a butyl, cyclohexyl, 4 - methyl - cyclohexyl, 2,5 - endomethylene-cyclohexyl or 2,5 - endomethylene - cyclohex - 3 - enyl group,

Y represents a —CH₂—CH₂— group,

Z represents a hydrogen atom or a chlorine atom in the 5-position to the carbonyl group,

Z' represents a hydrogen atom and phenylene represents an unsubstituted *p*-phenylene group.

3. A compound as claimed in claim 1, wherein R represents a hydrogen atom.

4. A compound as claimed in claim 1 or 3, wherein R¹ represents a cyclohexyl group.

5. A compound as claimed in claim 1 or 3, wherein R¹ represents a 4 - methyl-cyclohexyl group.

6. A compound as claimed in any one of claims 1 and 3 to 6, wherein Y represents a straight-chain, saturated hydrocarbon group containing 2 or 3 carbon atoms.

7. A compound as claimed in any one of claims 1 and 3 to 6, wherein Z and Z' each represents a hydrogen atom.

8. N - [4 - (β - Phthalimidino - α - methyl - ethyl) - benzenesulphonyl] - N' - cyclohexyl - urea.

205°C after recrystallization from methanol.

In an analogous manner there is obtained from 4 - (phthalimidino - methyl) - benzenesulphonamide and 4 - methyl - cyclohexyl isocyanate, N - [4 - (phthalimidino - methyl) - benzenesulphonyl] - N' - (4 - methyl - cyclohexyl) - urea melting at 191—193°C (from methanol).

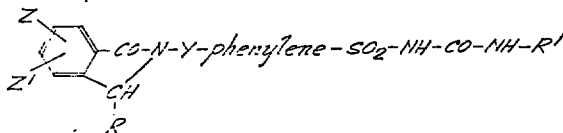
EXAMPLE 9:

N - [4 - (β - 3 - ethyl - phthalimidino - ethyl) - benzenesulphonyl] - N' - cyclohexyl-urea

7.6 grams of 4 - (β - 3 - ethyl - phthalimidino - ethyl) - benzenesulphonamide (melting point 215—217°C—prepared from 2 - β - phenylethyl - 3 - ethyl - phthalimidine by sulphochlorination and reaction with ammonia) and 6.2 grams of potassium carbonate are added to 100 cc of acetone. The mixture is heated at the boil under reflux for 1 hour while stirring. 2.8 grams of cyclohexyl isocyanate are then added dropwise, and stirring is continued for a further 3 hours at the boiling temperature. The reaction product is dissolved in water, the solution is filtered and the filtrate is acidified with dilute hydrochloric acid. The crystalline precipitate thus obtained is filtered with suction and dissolved in ammonia of 1% strength. Upon acidification with acetic acid, N - [4 - (β - ethyl - phthalimidino - ethyl) - benzenesulphonyl] - N' - cyclohexyl urea is obtained in good yield. It melts at 105—107°C.

WHAT WE CLAIM IS:—

1. A compound of the formula



in which

R represents a hydrogen atom or a methyl group,

R¹ represents

- (a) an alkyl group containing 3 or 4 carbon atoms,
- (b) a cyclohexyl-methyl group
- (c) an endoalkylene - cyclohexyl, endoalkylene - cyclohexenyl, endoalkylene - cyclohexyl - methyl or endoalkylene - cyclohexenyl - methyl group, each containing 1 or 2 endoalkylene carbon atoms,
- (d) a lower alkyl - cyclohexyl group,
- (e) a lower alkoxy - cyclohexyl group,
- (f) a cycloalkyl group containing 5 to 8 carbon atoms, or
- (g) a cyclohexenyl or cyclohexenyl-methyl group,

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

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

2. A compound of the formula given in claim 1 in which

Z represents a hydrogen atom or a methyl group,

R¹ represents a butyl, cyclohexyl, 4 - methyl - cyclohexyl, 2,5 - endomethylene-cyclohexyl or 2,5 - endomethylene - cyclohex - 3 - enyl group,

Y represents a —CH₂—CH₂— group,

Z represents a hydrogen atom or a chlorine atom in the 5-position to the carbonyl group,

Z' represents a hydrogen atom and phenylene represents an unsubstituted *p*-phenylene group.

3. A compound as claimed in claim 1, wherein R represents a hydrogen atom.

4. A compound as claimed in claim 1 or 3, wherein R¹ represents a cyclohexyl group.

5. A compound as claimed in claim 1 or 3, wherein R¹ represents a 4 - methyl-cyclohexyl group.

6. A compound as claimed in any one of claims 1 and 3 to 6, wherein Y represents a straight-chain, saturated hydrocarbon group containing 2 or 3 carbon atoms.

7. A compound as claimed in any one of claims 1 and 3 to 6, wherein Z and Z' each represents a hydrogen atom.

8. N - [4 - (β - Phthalimidino - α - methyl - ethyl) - benzenesulphonyl] - N'-cyclohexyl - urea.



9. N - [4 - (β - Phthalimidino - ethyl) - benzenesulphonyl] - N' - cyclohexyl-urea.
10. A physiologically tolerable salt of a compound as claimed in claim 1 with a base.
- 5 11. A physiologically tolerable salt of a compound as claimed in claim 2 with a base. 5
12. A physiologically tolerable salt of a compound as claimed in any one of claims 3 to 7 with a base.
- 10 13. A physiologically tolerable salt of the compound claimed in claim 8 or 9 with a base. 10
14. A compound as claimed in claim 1 and described in any one of the Examples herein.
- 15 15. A process for the manufacture of a compound as claimed in any one of claims 1 to 9, conducted substantially as hereinbefore described. 15
16. A pharmaceutical preparation which comprises a benzenesulphonyl urea as claimed in any one of claims 1 to 7 in admixture or conjunction with a pharmaceutically suitable carrier.
- 20 17. A pharmaceutical preparation which comprises the benzenesulphonyl - urea claimed in claim 8 or 9, in admixture or conjunction with a pharmaceutically suitable carrier. 20
18. A pharmaceutical preparation which comprises a salt as claimed in claim 10, 11 or 12, in admixture or conjunction with a pharmaceutically suitable carrier.
19. A pharmaceutical preparation which comprises a salt as claimed in claim 13, in admixture or conjunction with a pharmaceutically suitable carrier.
- 25 20. A pharmaceutical preparation as claimed in any one of claims 16 to 19, which is in a form suitable for oral administration. 25
21. A pharmaceutical preparation as claimed in any one of claims 16 to 20, which is in unit dosage form and contains up to 100 milligrams of the benzenesulphonyl urea or a physiologically tolerable salt thereof per unit dose.

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* C L M S *