United States Patent Office 3,729,462 Patented Apr. 24, 1973

3,729,462

p-AMINOALKYLBENZENESULFONAMIDE DERIVATIVES

Henri Dietrich, Arlesheim, Basel-Land, and Claude Lehmann, Basel, Switzerland, assignors to Ciba-Geigy Corporation

No Drawing. Filed Sept. 1, 1970, Ser. No. 68,793
Claims priority, application Switzerland, Sept. 4, 1969, 13,400/69
Int. Cl. C07d 49/30
U.S. Cl. 260—309.7 5 Claims

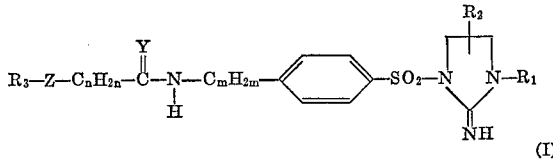
ABSTRACT OF THE DISCLOSURE

Compounds of the class of substituted 1-[p-(aminoalkyl)-phenylsulfonyl]-2-imino-imidazolidines and the pharmaceutically acceptable acid addition salts thereof have hypoglycemic activity; these compounds are active ingredients of pharmaceutical compositions and are useful for the treatment of diabetes mellitus; a typical embodiment is 1-[p-(2-ethoxyacetamidoethyl) - phenylsulfonyl]-2-imino-3-cyclohexyl-imidazolidine.

DETAILED DESCRIPTION

The present invention relates to derivatives of 1-[p-(aminoalkyl)-phenylsulfonyl]-2-imino-imidazolidines, to pharmaceutical compositions containing these compounds and to the use thereof.

More particularly, the present invention relates to compounds of formula



(I)

wherein

R_1 is alkyl having from one to six carbon atoms, alkenyl having from three to five carbon atoms, cycloalkyl or cycloalkenyl having from five to eight carbon atoms, or phenylalkyl having at most nine carbon atoms;
R_2 is hydrogen, methyl or ethyl;
R_3 is alkyl having from one to six carbon atoms;
m is the integer 2 or 3;
n is the integer 1, 2, 3, or 4;
y is oxygen or sulfur; and
Z is oxygen, sulfur, or a sulfoxide or sulfone grouping;

and the pharmaceutically acceptable acid addition salts thereof.

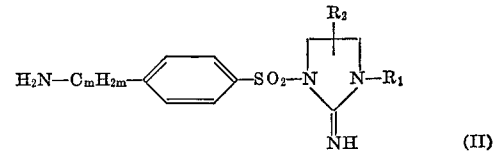
These compounds have been found to have a hypoglycemic effect in warm-blooded animals upon oral or parenteral administration. This activity, in combination with a favourable therapeutic index, characterizes the compounds of the present invention as being suitable for the treatment of diabetes mellitus.

The hypoglycemic action can be demonstrated in standard tests on experimental animals.

In the compounds of Formula I, R_1, as alkyl, can be the methyl, ethyl, propyl, isopropyl, butyl, sec.butyl, tert. butyl, isobutyl, pentyl, isopentyl, 2,2-dimethylpropyl, 1-methylbutyl, 1-ethylpropyl or the 1,2-dimethylpropyl group, or a straight-chained or branched hexyl radical, e.g. an n-hexyl radical, e.g. an n-hexyl, a methylpentyl, a dimethylbutyl, or an ethylbutyl group; as alkenyl, R_1 can be the allyl, 1-methylallyl, 2-methylallyl, the 2- or 3-butenyl or the 2-, 3- or 4-pentenyl group. As cycloalkyl, R_1 can be the cyclopentyl group which may be optionally substituted by alkyl radicals having one to three carbon atoms, the cyclohexyl group which may be substituted by ethyl or methyl, and the cycloheptyl group optionally substituted by methyl, as well as the cyclooctyl group. As cycloalkenyl, R_1 can be the 2-cyclopenten-1-yl, the 2-cyclohexen-1-yl, the 3-cyclohexene-1-yl, the 2-methyl-2-cyclohexen-1-yl, the 3-cyclohepten-1-yl group, or a cyclooctenyl group. As phenylalkyl, R_1 can be the benzyl, the phenylethyl or the α-methylphenylethyl group.

The substituent R_3 embraces the same alkyl groups as those given under R_1.

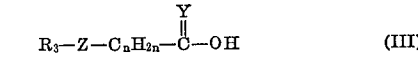
Using the process according to the invention, compounds of Formula I are produced by reacting an amine of formula



(II)

wherein

R_1, R_2 and m have the meanings given under Formula I, with a carboxylic acid or thiocarboxylic acid of formula



(III)

wherein

R_3 Z, n and Y have the meanings given under Formula I,

or with the reactive derivative of such a carboxylic acid or thiocarboxylic acid; and, optionally, converting the obtained reaction products into the salt of an inorganic or organic acid.

The reaction of an amine of Formula II with a carboxylic acid or thiocarboxylic acid of Formula III can be performed, e.g. by first converting the amine into the ammonium salt of an acid corresponding to Formula III; and then converting the ammonium salt, by dry heating, into the amide of Formula I. According to a preferred embodiment of the process according to the invention, an amine of Formula II is reacted with a carboxylic acid or thiocarboxylic acid of Formula III in the presence of a water-splitting agent in an inert solvent. A particularly suitable water-splitting agent is, e.g. N,N'-dicyclohexylcarbodiimide. As a water-splitting agent, it is also possible to use carbonyldipyrazole. Suitable inert solvents are, e.g. hydrocarbons such as benzene, toluene or xylene, ethers such as diethyl ether, dioxane or tetrahydrofuran, chlorinated hydrocarbons such as methylene chloride, chloroform, trichloroethylene and lower ketones such as acetone or methyl ethyl ketone.

Suitable reactive derivatives of a carboxylic acid or thiocarboxylic acid of Formula III are, e.g. halides, especially chlorides, lower alkyl esters, especially methyl or ethyl ester, phenyl ester, amides, lower mono- or dialkylamides, especially N-methylamides and N,N-dimethylamides, diphenylamides, also N-acylamides such as, e.g. acetylamides and benzoylamides.

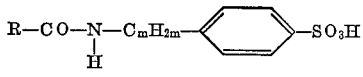
The reaction of the aforementioned reactive derivatives of carboxylic or thiocarboxylic acids is performed, e.g. at room temperature, or by heating, in one of the above already mentioned organic solvents. In general, the reaction may be carried out without the addition of condensation agents; optionally, however, such agents, e.g. alkali metal alcoholates and alkali metal hydroxides, can be added.

A halide of a carboxylic acid or thiocarboxylic acid of Formula III is reacted according to the invention preferably in the presence of an acid-binding agent. As acid-binding agents, it is possible to use inorganic bases or salts such as, e.g. an alkali hydroxide, alkali acetate, alkali hydrogen carbonate, alkali carbonate and alkali phosphate, such as sodium hydroxide, sodium acetate, sodium hy-

drogen carbonate, sodium carbonate and sodium phosphate, or the corresponding potassium compounds. It is also possible to use calcium oxide, calcium carbonate, as well as calcium phosphate and magnesium carbonate. Also suitable, in place of inorganic bases or salts, are organic bases such as, e.g. pyridine, trimethylamine or triethylamine, diisopropylamine, or collidine. Added in excess, these can also be used as solvent.

Instead of amines of Formula II, it is also possible to use, for the reaction according to the invention with a carboxylic acid or thiocarboxylic acid, N-alkali metal derivatives of these compounds such as, e.g. sodium, potassium or lithium derivatives.

The starting compounds of Formula II can be produced by one of several processes as described in Belgian Pat. 729,837. For example, one of these processes comprises adding a solution of a halide or the anhydride of a sulphonic acid of Formula IV:

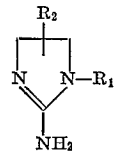


(IV)

wherein

R represents an alkyl radical or aryl radical, e.g. a methyl group or a phenyl group, and

R_4 and *m* have the meaning given in Formula I, in an inert solvent, especially a solution of the chloride in acetone to a 2-amino-2-imidazoline derivative of Formula V:

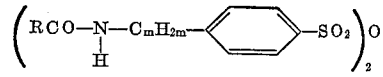


(V)

wherein

R_1 and R_2 have the meanings given under Formula I; in the presence of an acid binding agent, such as an aqueous alkali metal hydroxide solution, and then heating the mixture for a short time, and subsequently hydrolytically splitting off the protective acyl group (R—CO—), e.g. by refluxing the N-acyl compound obtained as intermediate product with 2 N hydrochloric acid for about 6 hours.

Suitable reactive derivatives of the sulphonic acids of Formula IV are halides, especially chlorides and anhydrides of Formula IVa:



(IVa)

The chlorides can be obtained substantially in accordance with E. Miller et al., J. Am. Chem. Soc. 62, 2099 (1940), or in accordance with U.S. Pat. No. 3,426,067, by reacting e.g. N-acetylphenethylamine or N-acetyl-α-methylphenethylamine with chlorosulfonic acid.

The anhydrides of Formula IVa can be obtained in a simple manner by reacting correspondingly substituted sulfonic acid halides with salts of the corresponding sulfonic acids.

The carboxylic acids or thiocarboxylic acids of the general Formula III can be obtained in a simple manner by reacting alcoholates or thiolates of Formula VI:

$$R_3—Z'—Me \qquad (VI)$$

wherein R_3 has the meaning given under Formula I, Z' denotes oxygen or sulphur, and Me denotes a monovalent metal,

with halogen-alkanoic acids or their lower alkyl esters Formula VII:

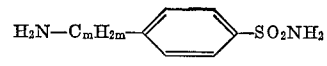
$$Hal—C_nH_{2n}—COOR \qquad (VII)$$

and, if an ester has been used as starting material, optionally saponifying this, and converting the obtained acid into another reactive derivative.

The carboxylic acids of Formula III (obtained with thiolates of Formula VI), in which Z represents a sulphur atom, can be converted by oxidation, e.g. with hydrogen peroxide or with potassium permanganate, into the corresponding carboxylic acids of Formula III, wherein Z represents the sulphoxide or sulphone grouping.

For the preparation of derivatives of carboxylic or thiocarboxylic acids of Formula III, wherein *n* is equal to 2, there is also the possibility of addition of corresponding alkanols or alkanethiols to acrylic acid derivatives.

Using a further process, starting materials of Formula II are obtained by reacting substituted p-(aminoalkyl)-benzenesulfonamides of formula



(VIII)

wherein *m* has the meaning given under Formula I, with substituted N-(2-bromoalkyl)-cyanamides in alkaline medium.

Compounds of Formula VIII are, in turn, obtained again substantially in accordance with E. Miller et al., J. Am. Chem. Soc. 62, 2099 (1940) by converting the chlorides of sulphonic acids of Formula IV with aqueous ammonia into the corresponding sulphonamides and finally splitting off the N-acyl groups by hydrolysis, e.g. refluxing in diluted hydrochloric acid.

The new substances, or the pharmaceutically acceptable salts thereof, can be administered orally or parenterally. For salt formation, it is possible to use suitable inorganic or organic acids such as, e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, acetic acid, lactic acid, succinic acid, tartaric acid and maleic acid, but also hypoglycemically active sulfonyl ureas such as, e.g. p-toluenesulfonylbutyl urea, p-chlorobenzenesulfonylpropyl urea and p-[2-(2-methoxy-5-chlorobenzamido) - ethyl] phenylsulfonyl-cyclohexyl urea.

For their intended use, the compounds of the invention are administered in amounts depending on the species, the age, weight and the particular condition of the individuals being treated and the mode of administration. In general, the daily dosage varies between about 0.1 and 100 mg./kg. of body weight for warm-blooded animals. Suitable dosage units, such as dragées and tablets, contain preferably 10–200 mg. of an active substance according to the invention, whereby the content of active substance is 20–80% by weight. The tablets and dragées are produced by combining the active substance, e.g. with solid pulverulent carriers such as lactose, saccharose, sorbitol or mannitol; starches such as potato starch, maize starch or amylopectin, also laminaria powder or citrus pulp powder; cellulose derivatives or gelatine, optionally with the addition of lubricants such as magnesium or calcium stearate or polyethylene glycols of suitable molecular weights. Tablets and dragée cores are coated, e.g. with concentrated sugar solutions which may also contain, e.g. gum arabic, talcum and/or titanium dioxide, or with a lacquer dissolved in readily volatile organic solvents or mixtures of solvents. Dyestuffs can be added to these coatings, e.g. for identification of the various dosages of active substance.

Other suitable dosage units for oral administration are hard gelatine capsules, as well as soft closed capsules made from gelatine and a softener, such as glycerin. The hard capsules contain the active substance preferably as a granulate, e.g. in admixture with fillers such as maize starch, and/or lubricants such as talcum or magnesium stearate, and optionally stabilisers such as sodium metabisulphite ($Na_2S_2O_5$) or ascorbic acid. In soft capsules, the active substance is preferably dissolved or suspended in suitable liquids such as liquid polyethylene glycols, whereby likewise stabilisers can be addedd.

The following prescriptions serve to further illustrate the production of tablets and dragées:

(a) An amount of 1000 g. of 1-[p-(2-ethoxyacetamidoethyl)-phenylsulphonyl]-2-imino - 3 cyclohexyl-imidazolidine is mixed with 500 g. of lactose and 270 g. of potato starch; the mixture is then moistened with an aqueous solution of 8.0 g. of gelatine, and granulated through a sieve. After drying of the granulate, 60.0 g. of potato starch, 60.0 g. of talcum, 10.0 g. of magnesium stearate and 20.0 of colloidal silicon dioxide are mixed in; the mixture is then pressed to form 10,000 tablets each weighing 200 mg. and each containing 100 mg. of active substance. Optionally, the tablets may be provided with grooves for a more precise adjustment of the dosage amount.

(b) A granulate is produced from 1000 g. of 1-[p-(2-ethoxyacetamidoethyl) - phenylsulphonyl] - 2 - imino-3-cyclohexyl-imidazolidine, 345 g. of lactose, and the aqueous solution of 6.0 g. of gelatine; the granulate is then mixed, after being dried, with 10.0 g. of colloidal silicon dioxide, 40.0 g. of talcum, 40.0 g. of potato starch and 5.0 g. of magnesium stearate; and the mixture is pressed into 10,000 dragée cores. These are subsequently coated with a concentrated syrup made from 533.0 g. of crystallised saccharose, 20.0 g. of shellac, 75.0 g. of gum arabic, 250 g. of talcum, 20 g. of colloidal silicon dioxide and 1.5 g. of dyestuff; and then dried. The obtained dragées each weigh 240 mg. and each contain 100 mg. of active substance.

The following examples further illustrate the production of the new compounds of Formula I and of intermediate products not described hitherto; the examples in no way constitute, however, the only embodiments thereof. The temperaturs are given in degrees centigrade.

Example 1

To a solution of 35.6 g. of 1-[p-(2-aminoethyl)-phenylsulphonyl] - 2-imino-3-methyl-imidazolidine dihydrochloride, M.P. 230–235°, in 100 ml. of water are added 150 ml. of 2-n sodium hydroxide solution; and the liberated base is extracted with methylene chloride. To the extract, dried with sodium sulphate, are added at 0° 20.6 g. of N,N'-dicyclohexylcarbodiimide. To the whole is then added dropwise at 0°, over 5 minutes, a solution of 9.0 g. of methoxyacetic acid in 30 ml. of methylene chloride. After 2 hours stirring at 0°, the precipitated N,N'-dicyclohexyl urea is filtered off, and the clear filtrate concentrated by evaporation. The thus obtained crude 1-[p-(2-methoxyacetamidoethyl)-phenylsulphonyl] - 2 - imino-3-methyl-imidazolidine is recrystallised from ethyl acetate/acetone. It contains 1½ moles of crystal water and melts at 159–160°.

In an analogous manner are obtained, within each case 20.6 g. of N,N'-dicyclohexylcarbodiimide and 9.0 g. of methoxyacetic acid, the following:

(a) From 38.2 g. of 1-[p-(2-aminoethyl)-phenylsulphonyl]-2-imino - 3 - allyl-imidazolidine dihydrochloride, M.P. 232–233°, is obtained: 1-[p-(2-methoxyacetamidoethyl)-phenylsulphonyl]-2-imino - 3 - allyl-imidazolidine, M.P. 103–104° (from ether/petroleum ether);

(b) From 39.8 g. of 1-[p-(2-aminoethyl)-phenylsulphonyl] - 2 - imino-3-butyl-imidazolidine dihydrochloride, M.P. 231–233°, is obtained: 1-[p-(2-methoxyacetamidoethyl)-phenylsulphonyl]-2-imino-3-butyl-imidazolidine;

(c) From 42.6 g. of 1-[p-(2-aminoethyl)-phenylsulphonyl] - 2 - imino-3-(1,2-dimethylbutyl)-imidazolidine dihydrochloride (crude product) is obtained: 1-[p-(2-methoxyacetamidoethyl)-phenylsulphonyl] - 2 - imino-3-(1,2-dimethylbutyl-imidazolidine, M.P. 137–138° (monohydrate; from ethyl acetate/acetone;

(d) From 41.0 g. of 1-[p-(2-aminoethyl)-phenylsulphonyl]-2-imino - 3 - cyclopentyl-imidazolidine dihydrochloride, M.P. 270°, is obtained: 1-[p-(2-methoxyacetamidoethyl)-phenylsulphonyl]-2-imino - 3 -cyclopentyl-imidazolidine, M.P. 151–151.5° (monohydarte; from ethyl acetate);

(e) From 42.4 g. of 1-[p-(2-aminoethyl)-phenylsulphonyl]-2-imino - 3 - cyclohexyl-imidazolidine dihydrochloride, M.P. 247–250°, is obtained: 1-[p-(2-methoxyacetamidoethyl)-phenylsulphonyl] - 2 - imino - 3 - cyclohexyl-imidazolidine, M.P. 150–151° (monohydrate; from ethyl acetate);

(f) From 43.8 g. of 1-[p-(2-aminoethyl)-phenylsulphonyl]-2-imino - 3 - (4-methylcyclohexyl)-imidazolidine dihydrochloride, M.P. 260°, is obtained: 1-[p-(2-methoxyacetamidoethyl)-phenylsulphonyl] - 2 - imino - 3 - (4-methylcyclohexyl)-imidazolidine, M.P. 159–160° (hemihydrate; from ethyl acetate).

Example 2

To a solution of 42.3 g. of 1-[p-(2-aminoethyl)-phenylsulphonyl] - 2 - imino-3-cyclohexyl-imidazolidine dihydrochloride, M.P. 247–250°, in 200 ml. of water are added 300 ml. of 2-n sodium hydroxide solution, and the whole is extracted with methylene chloride. To the extract dried with sodium sulphate are added 50.5 g. of triethylamine. An addition is then made dropwise at room temperature, within 20 minutes, of a solution of 13.5 g. of ethoxyacetyl chloride in 100 ml. of methylene chloride; the obtained mixture is then stirred for one hour at room temperature. The reaction solution is then washed first with 100 ml. of 2-n sodium hydroxide solution, and afterwards twice with 100 ml. of water. The combined aqueous phases are extracted twice with methylene chloride, and the obtained methylene chloride extracts combined with the washed reaction solution. By concentration by evaporation of the methylene chloride solution (dried with sodium sulphate) is obtained the crude 1-[p-(2-ethoxyacetamidoethyl)phenylsulphonyl]-2-imino-3-cyclohexyl-imidazolidine which, after recrystallization from ethyl acetate/petroleum ether, melts at 111–113°.

In ananalogous manner are obtained with, in each case, 50.5 g. of triethylamine:

(a) From 43.7 g. of 1-[p-(2-aminoethyl)-phenylsulphonyl]-2-imino-3-cyclopentyl-imidazolidine dihydrochloride, M.P. 270°, and 13.5 g. of ethoxyacetyl chloride: 1 - [p - (2 - ethoxyacetamidoethyl)-phenylsulphonyl]-2-imino - 3 - cyclopentyl-imidazolidine, M.P. 105–106.5° (from ethyl acetate);

(b) From 41.0 g. of 1-[p-(2-aminoethyl)-phenylsulphonyl] - 2 - imino - 3 - cyclopentyl-imidazolidine dihydrochloride, M.P. 270°, and 13.7 g. of methylthioacetic acid chloride: 1-[p-(2-methylmercaptoacetamidoethyl)-phenylsulphonyl]-2-imino - 3 - cyclopentyl-imidazolidine, M.P. 106–107° (purified by chromatography on the 20-fold amount of silica gel (grain size 0.05–0.2 mm.) with chloroform+5% methanol as solvent, and subsequent recrystallisation from ethyl acetate).

Example 3

An amount of 39.8 g. of 1-[p-(2-aminoethyl)-phenylsulphonyl] - 2 - imino-3-butyl-imidazolidine dihydrochloride, M.P. 231–233°, is suspended, with stirring, in a mixture of 500 ml. of methylene chloride and 100 ml. of 50% aqueous potassium carbonate solution. The mixture is stirred for 30 minutes. To the mixture, cooled with ice, is then added dropwise a solution of 17.0 g. of 2-ethylmercaptopropionic acid chloride in 100 ml. of methylene chloride, and stirring proceeds for a further 30 minutes. The organic phase is then separated, washed with water, and the methylene chloride evaporated off. The thus obtained 1-[p - (2-(2-ethylmercaptopropionamido)-ethyl)-phenylsulphonyl] - 2 - imino-3-butylimidazolidine melts, after recrystallisation from ethyl acetate, at 113–114°.

Example 4

An amount of 43.7 g. of 1-[p-(2-aminoethyl)-phenylsulphonyl] - 2 - imino-3-(4-methylcyclohexyl)-imidazolidine dihydrochloride, M.P. 260°, is suspended, with stir-

ring, in a mixture of 500 ml. of methylene chloride and 100 ml. of a 50% aqueous potassium hydroxide solution, and stirring then proceeds for a further 30 minutes. To the suspension, whilst it is being cooled with ice, is then added dropwise a solution of 15.0 g. of 2-methylmercaptopropionic acid chloride in 100 ml. of methylene chloride; stirring is continued for a further 30 minutes. The organic phase is separated, washed with water, and the methylene chloride evaporated off. The residue is dissolved in ethyl acetate, and the solution repeatedly extracted with 2-n hydrochloric acid. The combined acid extracts are made alkaline, whilst being cooled with ice, with conc. aqueous sodium hydroxide solution. The precipitated crude product is taken up with methylene chloride, the methylene chloride solution dried with sodium sulphate, and concentrated by evaporation. The thus obtained crude 1-[p-(2 - (2 - methylmercaptopropionamido) - ethyl)-phenylsulphonyl] - 2 - imino-3-(4-methylcyclohexyl)-imidazolidine is purified by recrystallisation from ethyl acetate. It melts at 157–158°.

In an analogous manner is obtained from 44.5 g. of 1-[p - (2 - aminoethyl) - phenylsulphonyl] - 2-imino-3-(2-phenylethyl)-imidazolidine dihydrochloride and 16.0 g. of 3-ethylmercaptopropionic acid chloride: 1-[p-(2-(3-ethylmercaptopropionamido) - ethyl) - phenylsulphonyl] - 2-imino-3-(2-phenylethyl)-imidazolidine.

Example 5

An amount of 41.5 g. of 1-[p-(2-aminoethyl)-phenylsulphonyl] - 2 - imino-3-isobutyl-imidazolidine dihydrochloride monohydrate, M.P. 151–152°, is suspended, with stirring, in a mixture of 500 ml. of methylene chloride and 100 ml. of 50% aqueous potassium hydroxide solution; stirring proceeds for a further 30 minutes. To the suspension, cooled with ice, is then added dropwise a solution of 17.0 g. of 3-ethylmercaptopropionic acid chloride in 100 ml. of methylene chloride; stirring continues for a further 30 minutes. The methylene chloride phase is separated, washed with water, and the methylene chloride evaporated off. The thus obtained crude 1-[p-(2-(3-ethylmercaptopropionamido) - ethyl) - phenysulphonyl]-2-imino-3-isobutyl-imidazolidine is purified by recrystallisation from ethyl acetate. It melts at 135–137°.

In an analogous manner are obtained:

(a) From 42.5 g. of 1-[p-(2-aminoethyl)-phenylsulphonyl] - 2 - imino - 3-(1,2-dimethylbutyl)-imidazolidine dihydrochloride and 15.0 g. of ethylmercaptoacetyl chloride: 1 - [p - 2 - ethylmercaptoacetamidoethyl)-phenylsulphonyl] - 2 - imino - 3-(1,2-dimethylbutyl)-imidazolidine, M.P. 75–78°. Purification of the crude product is performed by chromatography on the 20-fold amount of silica gel (grain-size 0.2–0.5 mm.) with chloroform+5% methanol as solvent, and subsequent recrystallisation from methylene chloride/ether;

(b) From 38.1 g. of 1-[p-(2-aminoethyl)-phenylsulphonyl] - 2 - imino-3-allyl-imidazolidine dihydrochloride, M.P. 232–233° and 14.5 g. of ethylmercaptoacetyl chloride: 1 - [p - (2 - ethylmercaptoacetamidoethyl)-phenylsulphonyl] - 2 - imino - 3-allyl-imidazolidine, M.P. 100–102° (purification by chromatography and recrystallisation analogously to (a)).

Example 6

To a solution of 42.3 g. of 1-[p-(2-aminoethyl)-phenylsulphonyl] - 2 - imino - 3-cyclohexyl-imidazolidine dihydrochloride, M.P. 247–250°, in 100 ml. of water are added 150 ml. of 2-n sodium hydroxide solution, and the free base is taken up in methylene chloride. To the methylene chloride solution dried with sodium sulphate are added portionwise at room temperature 36 g. of 3-methylmercaptopropionic acid and 60 g. of N,N'-dicyclohexylcarbodiimide. The solution is allowed to stand for 1 hour at room temperature, and is then concentrated by evaporation to dryness. The residue is shaken with a mixture of ethyl acetate and 2-n hydrochloric acid. The insoluble N,N'-dicyclohexyl urea is filtered off, the aqueous acid phase separated, and from this is then liberated the base, whilst ice cooling is applied, by the addition of concentrated aqueous sodium hydroxide solution; and it is taken up with methylene chloride. By concentration by evaporation of the methylene chloride solution (dried with sodium sulphate) is obtained crude 1-[p-(2-(3-methylmercaptopropionamido) - ethyl) - phenylsulphonyl]-2-imino-3-cyclohexyl - imidazolidine which, after recrystallisation from methylene chloride/ethyl acetate, melts at 160–162°.

The following is obtained in an analogous manner:

(a) From 37.1 g. of 1-[p-(2-aminoethyl)-phenylsulphonyl] - 2 - imino - 3-ethyl-imidazolidine dihydrochloride, M.P. 242–244°, 45.0 g. of 3-methylsulphonylpropionic acid and 60.0 g. of N.N'-dicyclohexylcarbondiimide is obtained: 1 - [p-(2-(3-methylsulphonylpropionamido)-ethyl) - phenylsulphonyl] - 2 - imino-3-ethyl-imidazolidine, M.P. 181–184° (from methanol/ether);

(b) From 39.7 g. of 1-[p-(2-aminoethyl)-phenylsulphonyl - 2 - imino-3-butyl-imidazolidine dihydrochloride, M.P. 231–233°, 50.0 g. of 3-ethylsulphonylpropionic acid and 60.0 g. of N,N'-dicyclohexylcarbodiimide is obtained: 1 - [p-(2-(3-ethylsulphonylpropionamido)-ethyl)-phenylsulphonyl]-2-imino-3-butyl-imidazolidine, M.P. 149–151° (from methanol).

Example 7

To a solution of 37.1 g. of 1-[p-(2-aminoethyl)phenylsulphonyl]-2-imino-3 - ethyl-imidazolidine dihydrochloride, M.P. 242–244°, in 100 ml. of water are added 150 ml. of 2-n sodium hydroxide solution, and the base is taken up with methylene chloride. The methylene chloride solution (dried with sodium sulphate) is concentrated by evaporation to dryness, and the residue dissolved in 300 ml. of tetrahydrofuran. To this soluiton are added portionwise, at room temperature, 36.0 g. of 3-methylmercapto-propionic acid and 60.0 g. of N,N'-dicyclohexylcarbodiimide; the solution is allowed to stand for 1 hour at room temperature, and is then concentrated by evaporation to dryness. The residue is treated analogously to Example 6. The obtained 1-[p-(2-(3-methylmercapto-propionamido)-ethyl) - 2-amino-3-ethyl-imidazolidine melts, after recrystallisation from ethyl acetate, at 137–139°.

Example 8

To a solution of 41.0 g. of 1-[p-(2-aminoethyl)-phenylsulphonyl] - 2 - imino-3-cyclopentyl-imidazolidine dihydrochloride, M.P. 270°, in 100 ml. of water are added 150 ml. of 2-n sodium hydroxide solution; and the base is taken with methylene chloride. The methylene chloride solution is dried with sodium sulphate, the methylene chloride distilled off, and the 1-[p-(2-aminoethyl)-phenylsulphonyl]-2-imino-3-cyclopentyl-imidazolidine remaining behind dissolved in 300 ml. of dioxane. To this solution are added portionwise, at room temperature, 45.0 g. of 3-methylsulphonyl-propionic acid and 60.0 g. of N,N'-dicyclohexylcarbodiimide. The solution is allowed to stand for 1 hour at room temperature, and is then concentrated by evaporation to dryness. The obtained residue is processed analogously to Example 6. By this means is obtained 1-[p-(2-(3-methylsulphonylpropionamido)-ethyl)-phenylsulphonyl] - 2-imino-3-cyclopentyl-imidazolidine, M.P. 180–181° (from methanol/ether).

Example 9

The base, liberated from a solution of 41.0 g. of 1-[p-(2-aminoethyl)phenylsulphonyl] - 2-imino-3-cyclopentyl-imidazolidine dihydrochloride, M.P. 270°, in 200 ml. of water by the addition of 300 ml. of 2-n sodium hydroxide solution, is taken up with methylene chloride; the methylene chloride solution is then dried with sodium sulphate, and the methylene chloride distilled off. The 1-[p-(2-aminoethyl)-phenylsulphonyl] - 2 - imino-3-cyclopentyl-imidazolidine remaining behind as oil is well mixed at

30–40°, under nitrogen, with 21.2 g. of methoxydithioacetic acid benzyl ester by shaking; the mixture is then heated for ½ hour in a water-bath to about 80°, whereby the colour of the dithio ester gradually disappears, and the product crystallises. The formed benzylmercaptan is afterwards removed by washing four times with 100 ml. of petroleum ether each time. The thus obtained crude 1-[p-(2-methoxythioacetamidoethyl) - phenylsulphonyl]-2-imido-3-cyclopentyl-imidazolidine melts, after recrystallisation from ethyl acetate, at 127–128°.

In an analogous manner is obtained, from 42.4 g. of 1-[p-(2-aminoethyl) - phenylsulphonyl] - 2-imino-3-cyclohexyl-imidazolidine dihydrochloride, M.P. 247–250°, and 21.2 g. of methoxydithioacetic acid benzyl ester: 1-[p-(2 - methoxythioacetamidoethyl) - phenylsulphonyl]-2-imno-3-cyclohexyl-imidazolidine, M.P. 146–147° (from acetone).

The methoxydithioacetic acid benzyl ester used as starting material can be obtained according to the following prescription:

An amount of 3.8 g. of hydrogen chloride is dissolved at —10° in a mixture of 7.1 g. of methoxyacetonitrile and 13.3 g. of benzylmercaptan; the solution is then allowed to stand for several days at —5° to —10° until it has been converted into a crystal cake. The formed methoxythioacetimidobenzyl ester hydrochloride is washed with petroleum ether, and dried in vacuo. The substance melts at 137–141° (decomposition).

Into a suspension of 23.2 g. of methoxythioacetimidobenzyl ester hydrochloride in 60 ml. of abs. pyridine is fed, whilst cooling is applied with an acetone/Dry Ice mixture, hydrogen sulphide until saturation is obtained. The temperature is then alowed to rise to 0°, and stirring proceeds for a further 1 hour at this temperature. To the whole are then added dropwise within 10 minutes, with ice cooling, 120 ml. of water; the formed emulsion is poured into a mixture of 270 ml. of conc. hydrochloric acid and 430 ml. of water, and the precipitated red-yellow oil is taken up with ether. The ethereal solution is washed with water, and dried with sodium sulphate. The crude methoxydithioacetic acid benzyl ester, remaining behind after the ether has been distilled off, is distilled in high vacuum, B.P. 110–120°/0.01 mm.

Example 10

Analogously to Example 1, with the use, each time, of 20.6 g. of N,N'-dicyclohexyl-carbodiimide, are obtained:

From 42.3 g. of 1-[p-(2-amino-ethyl)phenylsulphonyl] - 2-imino-3 - cyclohexyl-imidazolidine-dihydrochloride and 11.8 g. of propoxy-acetic acid, 1-[p-(2-propoxyacetamido)-ethyl-phenyl-sulphonyl] - 2-imno-3-cyclohexyl-imidazolidine, M.P. 100–102°;

From 42.3 g. of 1-[p-(2-amino-ethyl)-phenylsulphonyl]-2 - imino-3 - cyclohexyl-imidazolidine-dihydrochloride and 11.8 g. of isopropoxy-acetic acid, 1-[p-(2-isopropoxy-acetamido)-ethyl-phenyl-sulphonyl] - 2-imino-3-cyclohexyl-imidazolidine, M.P. 105–107°;

From 43.7 g. of 1-[p-(2-amino-ethyl)-phenylsulphonyl]-2 - imino-3- - (2-methyl-cyclohexyl)-imidazoline-dihydrochloride and 10.4 g. of 3-methoxy-propionic acid, 1-[p-(3 - methoxy-propionamido)-ethyl - phenylsulphonly]-2-amino-3-(2-methyl-cyclohexyl)-imidazoline, M.P. 130 to 132°;

From 43.2 g. of 1-[p-(2-amino-ethyl)-phenylsulphonyl]-2-imino - 3 - cyclohexyl-imidazolidine-dihydrochloride and 11.8 g. of 3-ethoxy-propionic acid, 1-[p-(2-(3 - ethoxy-propionamido)-ethyl)-phenylsulphonyl]-2-imino-3-cyclohexyl-imidazolidine, M.P. 130–132°;

From 43.7 g. of 1-[p-(2 - amino - ethyl) - phenylsulphonyl]-2-imino - 3 - (2 - methyl - cyclohexyl) - imidazolidine-dihydrochloride and 13.2 g. of 3-isopropoxy-propionic acid, 1 - [p - (2 - (3 - isopropoxy - propionamido)-ethyl) - phenylsulphonyl] - 2 - imino - 3 - (2 - methyl-cyclohexyl)-imidazolidine, M.P. 128–130°;

From 42.3 g. of 1-[p-(2-amino - ethyl) - phenylsulphonyl]-2-imino - 3 - cyclohexyl - imidazolidine - dihydrochloride and 10.6 g. of methylmercapto-acetic acid, 1-[p-(2-methylmercaptoacetamido - ethyl) - phenylsulphonyl]-2-imino-3-cyclohexyl-imidazolidine, M.P. 120–121°;

From 39.7 g. of 1-[p-2-amino-ethyl)phenylsulphonyl]-2-imino-3-sec.butyl - imidazolidine - dihydrochloride and 10.6 g. of methylmercapto-acetic acid, 1-[p-(2-methylmercapto-acetamido)-ethyl)-phenylsulphonyl] - 2 - imino-3-sec.butyl-imidazolidine, M.P. 104–105°;

From 42.3 g. of 1-[p-(2-amino-ethyl) - phenylsulphonyl]-2-imino - 3 - cyclohexyl - imidazolidine - dihydrochloride and 12.0 g. of ethylmercapto-acetic acid, 1-[p-(2-ethylmercaptoacetamido)-ethyl) - phenylsulphonyl]-2-imino-3-cyclohexyl-imidazolidine, M.P. 128–130°;

From 39.7 g. of 1-[p-(2-amino-ethyl) - phenylsulphonyl]-2-imino-3-sec.butyl - imidazolidine - dihydrochloride and 10.6 g. of methylmercapto-acetic acid, 1-[p-(2-(2-methylmercapto-propionamido) - ethyl) - phenylsulphonyl]-2-imino-3-sec.butyl-imidazolidine, M.P. 113–115°;

From 40.9 g. of 1-[p-(2-amino - ethyl) - phenylsulphonyl]-2-imino-3-cyclopentyl - imidazolidine - dihydrochloride and 10.6 g. of 3-methylmercapto-propionic acid, 1-[p-(2-(3-methylmercapto-propionamido) - phenylsulphonyl]-2-imino-3-cyclopentyl-imidazolidine, M.P. 132–133°;

From 42.3 g. of 1-[p-(2-amino-ethyl) - phenylsulphonyl]-2-imino-3-cyclohexyl - imidazolidine - dihydrochloride and 16.2 g. of 3-tert.butylmercapto-propionic acid, 1-[p-(2 - (3 - tert.butylmercapto-propionamido) - ethyl)-phenylsulphonyl]-2-imino-3 - cyclohexyl - imidazolidine, M.P. 142–146°;

From 42.3 g. of 1-[p-(2-amino - ethyl) - phenylsulphonyl]-2-imino-3-cyclohexyl-imidazolidine - dihydrochloride and 13.4 g. of propylmercapto-acetic acid, 1-[p-(2-propylmercapto-acetamido)-ethyl)-phenylsulphonyl] - 2 - imino-3-cyclohexyl-imidazolidine, M.P. 110–111°;

From 42.3 g. of 1-[p-(2-amino - ethyl) - phenylsulphonyl]-2-imino-3-cyclohexyl-imidazolidine - dihydrochloride and 13.4 g. of isopropylmercapto-acetic acid, 1-[p-(2-isopropylmercapto-acetamido) - ethyl) - phenylsulphonyl]-2-imino-3-cyclohexyl-imidazolidine, M.P. 125–126°;

From 42.3 g. of 1-[p-(2-amino - ethyl) - phenylsulphonyl]-2-imino-3-cyclohexyl-imidazolidine - dihydrochloride and 14.8 g. of tert.butylmercapto-acetic acid, 1 - [p - (2-(tert.butylmercapto - acetamido) - ethyl) - phenylsulphonyl]-2-imino-3-cyclohexyl-imidazolidine, M.P. 140–141°;

From 35.5 g. of 1-[p-(2-amino - ethyl) - phenylsulphonyl]-2-imino-3-methyl-imidazolidine - dihydrochloride and 13.4 g. of 2-ethylmercapto-propionic acid, 1-[p - (2 - (2-ethylmercapto-propionamido)-ethyl) - phenylsulphonyl]-2-imino-3-methyl-imidazolidine, M.P. 140–142°;

From 39.7 g. of 1-[p-(2-amino - ethyl) - phenylsulphonyl]-2-imino-3-isobutyl - imidazolidine - dihydrochloride and 16.6 g. of 3-ethylsulphonyl-propionic acid, 1-[-(2-(3-ethylsulphonyl - propionamido) - ethyl) - phenylsulphonyl]-2-imino-3-isobutyl-imidazolidine, M.P. 176–177°;

From 40.9 g. of 1-[p-(2-amino - ethyl) - phenylsulphonyl]-2-imino-3 - cyclopentyl - imidazolidine - dihydrochloride and 13.4 g. of methylsulphonyl-acetic acid, 1-[p-(2-(methylsulphonyl-acetamido) - ethyl) - phenylsulphonyl]-2-imino-3-cyclopentyl-imidazolidine, M.P. 147°;

From 42.3 g. of 1-[p-(2-amino - ethyl) - phenylsulphonyl]-2-imino-3-cyclohexyl-imidazolidine - dihydrochloride and 15.2 g. of ethylsulphonyl-acetic acid, 1-[p-(2-ethylsulphonyl-acetamido)-ethyl)-phenylsulphonyl] - 2 - imino-3-cyclohexyl-imidazolidine, M.P. 144–146°;

From 35.5 g. of 1-[p-(2-amino-ethyl) - phenylsulphonyl]-2-imino-3-methylimidazolidine - dihydrochloride and 16.6 g. of 2-ethylsulphonyl-propionic acid, 1-[p-(2-(2-ethylsulphonyl-propionamido)-ethyl) - phenylsulphonyl]-2-imino-3-methylimidazolidine, M.P. 162–163°;

From 39.7 g. of 1-[p-(2-amino - ethyl) - phenylsulphonyl]-2-imino-3-isobutyl-imidazolidine-dihydrochloride and 15.0 g. of 3-ethylsulphinyl-propionic acid, 1-[p-(2-(3-

ethylsulphinyl-propionamido) - ethyl) - phenylsulphonyl]-2-imino-3-isobutyl-imidazolidine, M.P. 141–143°;

From 40.9 g. of 1-[p-(2-amino - ethyl) - phenylsulphonyl]-2-imino-3-cyclopentyl - imidazolidine - dihydrochloride and 12.2 g. of methylsulphinyl-acetic acid, 1-[p-(2-(methylsulphinyl)-acetamido)-ethyl) - phenylsulphonyl]-2-imino-3-cyclopentyl-imidazolidine, M.P. 141–142°;

From 40.9 g. of 1-[p-(2-amino - ethyl) - phenylsulphonyl]-2-imino-3-cyclopentyl - imidazolidine - dihydrochloride and 13.6 g. of 3-methylsulphinyl-propionic acid, 1-[p-(2-(3-methylsulphinyl-propionamido)-ethyl) - phenylsulphonyl]-2-imino - 3 - cyclopentyl - imidazolidine, M.P. 146–147°;

From 42.3 g. of 1-[p-(2-amino - ethyl) - phenylsulphonyl]-2-imino-3-cyclohexyl-imidazolidine - dihydrochloride and 13.6 g. of ethylsulphinyl acetic acid, 1-[p-(2-ethylsulphinyl-acetamido)-ethyl)-phenylsulphonyl] - 2 - imino-3-cyclohexyl-imidazolidine, M.P. 133–134°;

From 42.3 g. of 1-[p-(2-amino - ethyl) - phenylsulphonyl]-2-imino-3-cyclohexyl-imidazolidine - dihydrochloride and 17.8 g. of 3-tert.butylsulphinyl-propionic acid, 1-[p-(2-(3-tert.butylsulphinyl-propionamido) - ethyl) - phenylsulphonyl]-2-imino-3-cyclohexyl-imidazolidine, M.P. 125–127°;

From 43.7 g. of 1-[p-(2-amino-propyl) - phenylsulphonyl]-2-imino-3-cyclohexyl-imidazolidine - dihydrochloride and 9.0 g. of methoxy-acetic acid, 1-[p-(2-methoxy-acetamido)-propyl-phenylsulphonyl]-2-imino - 3 - cyclohexyl-imidazolidine, M.P. 120–121°;

From 43.7 g. of 1-[p-(2-amino - ethyl) - phenylsulphonyl]-2-imino-3-cyclohexyl-4 - methyl - imidazolidine-dihydrochloride and 10.4 g. of ethoxy-acetic acid, 1-[p-(2-ethoxy-acetamido)-ethyl)-phenylsulphonyl] - 2 - imino-3-cyclohexyl-4-methyl-imidazolidine, M.P. 115–117°;

From 43.7 g. of 1-[p-(2-amino - ethyl) - phenylsulphonyl]-2-imino-3-cyclopentyl-4-ethyl - imidazolidine - dihydrochloride and 13.4 g. of 3-ethylmercapto-propionic acid, 1-[p-(2-(3-ethylmercapto-propionamido)-ethyl) - phenylsulphonyl]-2-imino-3-cyclopentyl-4 - ethyl - imidazolidine, an oil;

From 43.7 g. of 1-[p-(2 - amino - ethyl)-phenylsulphonyl]-2-imino - 3 - cycloheptyl-imidazolidine-dihydrochloride and 12.0 g. of 2-methylmercapto-propionic acid, 1-[p-(2-(2 - methylmercapto - propionamido) - ethyl)-phenylsulphonyl]-2-imino - 3 - cycloheptyl-imidazolidine, M.P. 167–169°;

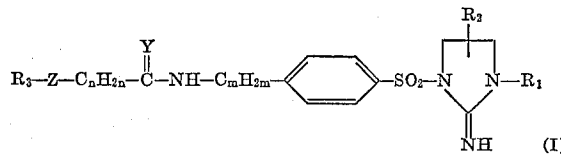
From 43.1 g. of 1-[p-(2-amino-ethyl)-phenylsulphonyl]-2-imino - 3 - benzyl-imidazolidine-dihydrochloride and 12.0 g. of 2-methyl-mercapto-propionic acid, 1-[p - (2-(2-methyl-mercapto - propionamido) - ethyl) - phenylsulphenyl]2-imino-3-benzyl-imidazolidine, M.P. 141–143°;

From 44.5 g. of 1-[p-(2-amino-ethyl)-phenylsulphonyl]-2-imino - 3 - (β-phenyl-ethyl)-imidazolidine-dihydrochloride und 13.4 g. of 3-ethylmercapto-propionic acid, 1-[p-(2-(3-ethylmercapto - propionamido) - ethyl)-phenylsulphonyl] - 2 - imino-3-(β-phenyl-ethyl)-imidazolidine, M.P. 102–103°;

From 42.1 g. of 1-[p-(2 - amino-ethyl) - phenylsulphonyl]-imino - 3 - (3 - cyclohexen-1-yl)-imidazoline-dihydrochloride and 9.0 g. methoxy-acetic acid, 1-[p-2-methoxy-acetamido)-ethyl)-phenylsulphonyl] - 2 - imino-3-(3-cyclohexen-1-yl)-imidazolidine.

What is claimed is:

1. A compound of formula



(I)

wherein

R_1 is alkyl of from one to six carbon atoms; alkenyl of from three to five carbon atoms; cycloalkyl, cycloalkenyl, alkyl substituted cycloalkyl or alkyl substituted cycloalkenyl of from five to eight carbon atoms; or phenylalkyl of at most three carbon atoms in the alkyl chain;

R_2 is hydrogen, methyl or ethyl;

R_3 is alkyl of from one to six carbon atoms;

m is the integer 2 or 3;

n is the integer 1, 2, 3 or 4;

Y is oxygen or sulfur; and

Z is oxygen, sulfur or a sulfoxide or sulfone grouping,

or the pharmaceutically acceptable acid addition salts thereof.

2. A compound according to claim **1**, which is 1-[p-(2 - ethoxyacetamidoethyl) - phenylsulfonyl]-2-imino-3-cyclohexyl-imidazolidine.

3. A compound according to claim **1**, which is 1-[p-(2-(3-ethylmercaptopropionamido) - ethyl) - phenylsulfonyl]-2-imino-3-isobutyl-imidazolidine.

4. A compound according to claim **1**, which is 1-[p-(3-methylmercaptopropionamido) - ethyl) - phenylsulfonyl]-2-imino-3-cyclohexyl-imidazolidine.

5. A compound according to claim **1**, which is 1-[p-(2-(3-ethoxypropionamido) - ethyl) - phenylsulfonyl]-2-imino-3-cyclohexyl-imidazolidine.

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NATALIE TROUSOF, Primary Examiner

U.S. Cl. X.R.

260—455 R, 481 R, 526 S, 535 R, 543 R, 544 Y, 545 R, 551 R, 556 Hr, 558 R, 558 S, 561 S, 561 B, 562 R, 562 S; 424—273