(41)

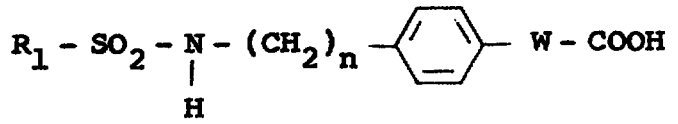
New sulphonamides, processes for their preparation, as well as medicaments containing these compounds

The present invention concerns sulphonamidoalkylphenylcarboxylic acids and their derivatives, processes for their preparation, as well as medicaments which contain these compounds.

From J. Med. Chem. 21, 673 et seq. (1978) are known 4-tosylamidomethylbenzoic acid ethyl ester, from J. Med. Chem. 22, 862 et seq. (1979) further 4-tosylamidomethylbenzoic acid derivatives and from U.S. 4,112,236 some 4-alkylsulphonamidoalkylbenzoic acid derivatives, especially 4-(3-methanesulphonamidopropyl)-benzoic acid ethyl ester, as intermediate product, without indication of a pharmacological action.

In DE-OS 2604560 and in DE-OS 2532420 are described phenylcarboxylic acids which are substituted in the 4-position by a carbonamide group as blood sugar-sinking and lipid-sinking substances. Surprisingly, it has now been found that analogous phenylcarboxylic acids which are substituted in the 4-position by a sulphonamide group show not only an excellent lipid-sinking action but also an outstanding inhibiting action of thrombocyte aggregation.

Therefore, the subject of the present invention are new sulphonamides of the general formula I



(I)

in which R_1 signifies an aryl, aralkyl or aralkenyl group, wherein the alkyl radical of the aralkyl group contains 1-5 C-atoms and the alkenyl radical or the aralkenyl group 2-3 C-atoms, and whereby the aryl radical signifies an aromatic hydrocarbon with 6-12 C-atoms which can possibly be substituted one or more times by hydroxyl, halogen, trifluoromethyl, lower alkyl or lower alkoxy with 1-5 C-atoms or acetyl, n the numbers 2 and 3, W represents a bond or an unbranched or branched alkylene chain with 1-4 C-atoms which is either saturated or contains a double bond, as well as their physiologically acceptable salts, esters and amides.

By "lower alkyl" and "lower alkoxy groups" are to be understood not only straight-chained but also branched radicals. As straight-chained lower alkyl radicals, there preferably finds use the methyl group, as branched lower alkyl radical the tert.-butyl group and as lower alkoxy group the methoxy group.

As aralkyl radicals, those come into question, the alkyl radicals of which are straight-chained or branched. The phenethyl and the 4-chlorophenethyl radical are preferred.

As aralkenyl radical, the styryl and the 4-chlorostyryl radical are preferred.

By "aryl radical" are especially to be understood the phenyl, the diphenylyl and the naphthyl radical. These aryl radicals can be substituted in all possible positions as stated.

By halogen, one preferably understands fluorine, chlorine and bromine.

By unbranched alkylene groups W are to be understood the following:

$-CH_2-$ $-(CH_2)_2-$ and $-(CH_2)_3-$ (saturated)

as well as

$-CH=CH-$ (unsaturated).

As branched groups W are preferably claimed the groups:

$$-\underset{\displaystyle CH_3}{\overset{\displaystyle |}{CH}}- \qquad -\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\overset{\displaystyle |}{\underset{\displaystyle |}{C}}}}- \qquad \text{and} \qquad -CH_2\underset{\displaystyle CH_3}{\overset{\displaystyle |}{CH}}- \qquad \text{(saturated)}$$

as well as

$$-\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}=CH- \qquad \text{and} \qquad -CH=\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}- \qquad \text{(unsaturated)}$$

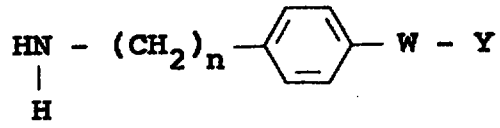
The esters derived from the carboxylic acids of the general formula I contain, as alcohol components, lower monohydroxyl alcohols of which methanol, ethanol and n-butanol are preferred, as well as polyhydroxy alcohols, e.g. glycol or glycerol, or alcohols with other functional groups, such as e.g. ethanolamine or glycol ethers.

The amides according to the invention derived from the carboxylic acids of the general formula I contain, as amine component, e.g. ammonia, p-aminobenzoic acid, β-alanine, ethanolamine or 2-aminopropanol, whereby those previously mentioned are to be preferred. However, there also come into question alkylamines such as e.g. isopropylamine or tert.-butylamine, dialkylamines, such as diethylamine, as well as cyclic amines, such as e.g. morpholine or 4-alkyl- or -arylpiperazines, e.g. 4-methylpiperazine, 4-(4-chlorobenzyl)-piperazine or 4-(3-methoxyphenyl)-piperazine.

The above definition of the compounds according to the invention is also to include all possible stereoisomers, as well as their mixtures.

Furthermore, the subject of the present invention are processes for the preparation of sulphonamides of the general formula I, in which R, R_1, n and W have the given meaning, in that, for example, one

a) reacts an amine of the general formula II



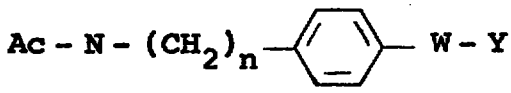
(II)

in which n and W here and in all following examples have the above-given meaning and Y here and in all following examples signifies the group $-COOR_2$, in which R_2 signifies a hydrogen atom or a lower alkyl group, an acid amide group or a residue which, after condensation

has taken place, is converted into the $COOR_2$ group or into an acid amide group, in per se known manner with a sulphonic acid of the general formula III

$$R_1 - SO_2OH \qquad (III)$$

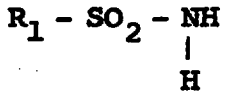
in which R_1 here and in all following examples has the above-given meaning, or a derivative thereof, or, instead of the free amines II, uses their salts; or - as a variant of this process - carries out a transacylation which then takes place when one reacts a free sulphonic acid III with a compound of the general formula IV



$$Ac - N(H) - (CH_2)_n - C_6H_4 - W - Y \qquad (IV)$$

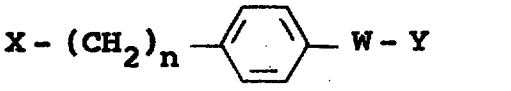
in which Ac represents an easily exchangeable acyl radical, in a suitable solvent; or

b) reacts a sulphoamide of the general formula V



$$R_1 - SO_2 - NH(H) \qquad (V)$$

with a compound of the general formula VI

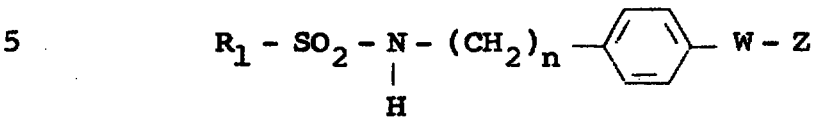


$$X - (CH_2)_n - C_6H_4 - W - Y \qquad (VI)$$

whereby X here and in all following examples is to represent a reactive group, subsequent to the reactions having taken place possibly converts the acid derivatives obtained of the general formula I into the free

acids or, if desired, the free acids obtained of the general formula I into an ester, into an amide or into a physiologically acceptable salt; or

c) oxidises a compound of the general formula VII

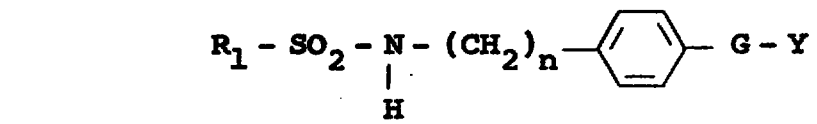


(VII)

in which Z represents a residue oxidatively convertible into the carboxyl group.

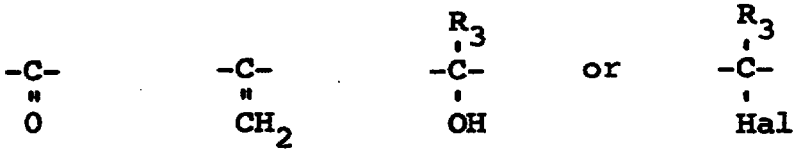
Further processes for the preparation of the compounds according to the invention consist in that one

d) reduces a compound of the general formula VIII



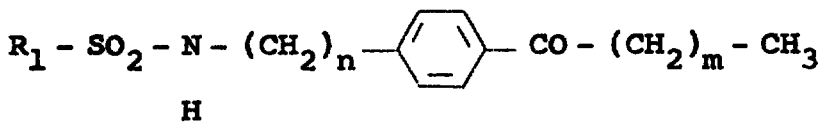
(VIII)

in which G represents a carbon chain which contains one of the groups



or possibly functional derivatives of these groups; or, for the case in which W represents an unbranched chain,

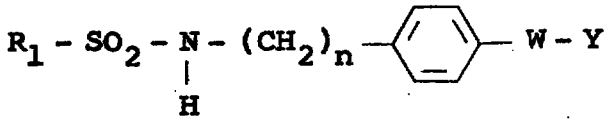
e) reacts a compound of the general formula IX



(IX)

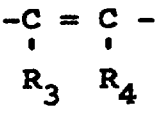
in which m represents the numbers 0 to 2, under the conditions of a possibly modified Willgerodt-Kindler reaction.

f) for the preparation of compounds of the general formula X



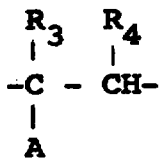
(X)

in which W has the special meaning

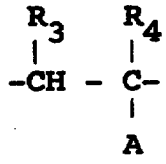


there come into question all conventional processes for the preparation of cinnamic acids of of their derivatives:

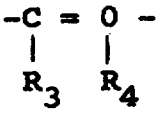
f 1) In the case of the presence of suitable compounds X in which W has the meaning



or

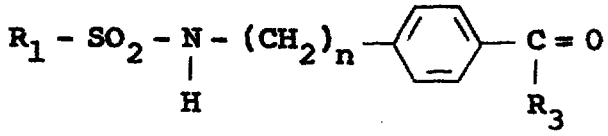


whereby A represents a halogen atom, a hydroxyl group or a functionally changed hydroxyl group, one gets to the desired compounds X, in which W represents the group



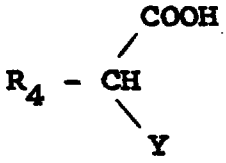
by action of an agent splitting off HA.

f 2) In the case of the presence of suitable compounds XI



(XI)

one can prepare the desired cinnamic acid derivatives by reactions in the manner of an aldol condensation, i.e. by reactions with activated CH groups. As such compounds, there come into question acetic acid or its derivatives, but especially malonic acid derivatives of the general formula XII



(XII)

whereby, in the latter case, after condensation has taken place, a decarboxylation occurs.

As further possibility of such aldol-like reactions, there is mentioned the Perkin reaction which consists of a reaction of compounds of the general formula XI with the anhydride of an aliphatic carboxylic acid in the presence of an alkali metal salt, possibly of the same carboxylic acid.

f 3) A third possibility consists in the reaction of compounds of the general formula XI with suitable phospho-organic compounds in the manner of modified Wittig reactions. As such phospho-organic reaction partners, there may be mentioned e.g. the alkoxy-

carbonylmethylphosphonic acid alkyl esters of the general formula XIII

$$(Alk\text{-}O)_2\text{-}PO\text{-}\underset{\displaystyle R_4}{\underset{|}{CH}}\text{-}COO\text{-}Alk \qquad (XIII)$$

g) By hydrogenation of the cinnamic acid derivatives obtained according to methods f1 to 3 or according to other methods, there can be prepared the analogous compounds with saturated carbon chain.

As reactive derivatives of the sulphonic acids III there come into question especially the halides, as well as the esters. The reactions of the sulphonic acid halides with compounds of the general formula II expediently takes place with the addition of an acid-binding agent, such as e.g. alkali metal acetate, sodium hydrogen carbonate, sodium carbonate, sodium phosphate, calcium oxide, calcium carbonate or magnesium carbonate. However, this function can also be undertaken by organic bases, such as e.g. pyridine or triethylamine, whereby, as inert solvent, there serves e.g. ether, benzene, methylene chloride, dioxan or an excess of the tertiary amine.

In the case of the use of inorganic acid binders, as reaction medium one uses e.g. water, aqueous ethanol or aqueous dioxan.

The transacylation reaction between a free sulphonic acid III and an acylamine IV is carried out with the use of preferably equimolar amounts of both

reaction partners in a polar solvent. As such polar solvents, there serve e.g. alcohols, especially ethanol and methanol. The reaction preferably proceeds at the boiling temperature of this solvent. As easily exchangeable acyl radical, there is to be mentioned e.g. the acetyl radical.

For the alkylation of the sulphonamides V one preferably uses compounds VI in which X represents an arylsulphonyloxy group. Preferably, X is to signify a toluenesulphonyloxy group. Thus, as alkylation agents, there preferably serve arylsulphonic acid alkyl esters, a method which is described in its application to sulphonic acid amides e.g. by Klamann et al., Monatshefte für Chemie, Vol. 83 (1952), p. 871. The reaction takes place in alkaline medium, the preferred reaction medium being hot, concentrated soda solution.

As oxidisable groups which can be converted into a carboxyl function, there preferably come into question the hydroxymethyl, the aminomethyl and the formyl group, possibly also the acetyl group or functional derivatives of these groups. The oxidation can be carried out with the usual oxidation agents, such as e.g. manganese IV compounds, permanganates, dichromates, in the case of the formyl group also with atmospheric oxygen or silver oxide, but in the case of the acetyl group, e.g. with hypobromite.

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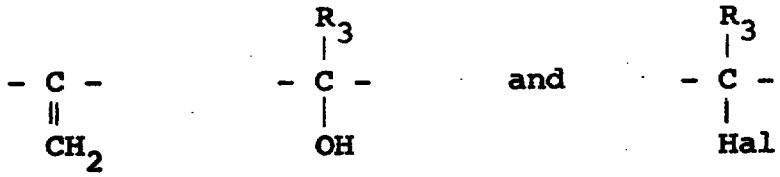
For the reduction of the groups G contained in the general formula VIII, numerous processes are suitable. The reduction of the group -CO- can take place e.g. according to Clemmensen by means of zinc/ hydrochloric acid. However, the reduction with hydrogen at normal pressure or at elevated pressure in the presence of metal catalysts, such as e.g. palladium or platinum, in solvents, such as e.g. acetic acid or lower alcohols, is preferred.

Also the groups



are preferably reduced by catalytically activated hydrogen, whereby the group G containing a hydroxyl group can best be reduced in the presence of strong acids. The presence of sulphuric acid or perchloric acid in catalytic amounts is hereby preferred. One can possibly also reduce with complex metal hydrides. Sodium borohydride is preferably used. In this case, the reaction can be carried out in an alcohol, especially in methanol, or in dioxan or in aqueous-alkaline medium.

The ketones of the general formula IX employed in the case of process e can easily be prepared by Friedel-Crafts acylation. They are reacted with sulphur and a secondary amine, preferably with morpholine. The

thiomorpholide resulting in the case of this "Willgerodt-Kindler reaction" is saponified in per se known manner with the help of strong alkali lyes or with strong hydrochloric acid or also with a mixture of sulphuric acid, glacial acetic acid and water to the carboxylic acid.

For the preparation of cinnamic acid derivatives according to process f 1), there are suitable all processes which permit a splitting off of HA. If A represents a hydroxyl group, then a dehydration can take place with the usual agents, such as e.g. glacial acetic acid, acetic anhydride, sulphuric acid, hydrogen sulphate, polyphosphoric acid, phosphorus oxychloride, thionyl chloride or phosphorus pentoxide, whereby one expediently works in inert solvents, such as benzene, methylene chloride, carbon tetrachloride and the like. A dehydration with phosphorus pentoxide in boiling methylene chloride is preferred. The hydroxy compounds necessary for the dehydration can be prepared e.g. by a Reformatzky reaction from the corresponding aldehydes or ketones or one obtains them by reduction of the corresponding keto compounds either with complex hydrides, such as e.g. sodium borohydride, or by hydrogenation with Raney nickel as catalyst.

For the splitting off of hydrogen halide (when A signifies a halogen atom), there come into question basic agents. Suitable basic agents are e.g. inorganic

or organic bases, such as NaOH, KOH, sodium acetate, Na_2CO_3, as well as alcoholates, such as sodium methylate, amines, such as e.g. triethylamine, dimethylaniline and pyridine. One expediently works in inert solvents, such as dioxan, DMSO, benzene, petroleum ether or alcohols, such as ethanol or isopropanol.

The condensation of compounds of the general formula XI with malonic acid derivatives takes place in known manner by reaction of both partners in suitable solvents, such as e.g. pyridine, preferably in the presence of a primary or secondary amine, whereby, as secondary amine, piperidine is preferred.

The reactions between compounds XI with phosphonic acid esters (PO-activated olefin formation according to Horner) is carried out in inert solvents in the presence of bases. As inert solvents, there are suitable e.g. diglyme, benzene, toluene, THF, DMF, but also ethers and petroleum ether. Suitable bases are e.g. sodium amide, organo-lithium compounds, alcoholates (mostly dissolved in the corresponding alcohol), sodium hydride, as well as dimethyl sulphoxylate in DMSO. The reactions are carried out either at room temperature or at elevated temperatures (boiling temperature of the solvent).

As substituents Y of the general formula IV, which can be converted into the $-COOR_2$ group, there come into question, for example, the nitrile, carbaldehyde, hydroxymethyl, aminomethyl and formyl group.

The conversion of the substituents R_2 possibly to be carried out subsequent to the condensation takes place, for example, by saponification of the carboxylic acid esters (R_2 = alkyl) to the corresponding carboxylic acids (R_2 = hydrogen) with mineral acids or alkali metal hydroxides in polar solvents (such as water, methanol, ethanol, dioxan or acetone). The saponification is advantageously carried out with a strong base (such as sodium or potassium hydroxide) in a mixture of methanol and water at room temperature or moderately elevated temperature. On the other hand, however, one can also esterify the carboxylic acids in the usual way or convert esters with a particular radical R_2 into an ester with another radical R_2 by transesterification. The esterification of the carboxylic acids is expediently carried out in the presence of an acidic catalyst, such as e.g. hydrogen chloride, sulphuric acid, p-toluenesulphonic acid or of a strongly acidic ion exchanger resin. Transesterifications, on the other hand, require the addition of a small amount of a basic substance, e.g. of an alkali metal or alkaline earth metal hydroxide or of an alkali metal alcoholate. For the esterification of the carboxylic group or for a transesterification, in principle all alcohols are suitable. There are preferred the lower monohydroxy alcohols, such as methanol, ethanol or propanol, as well as polyhydroxy alcohols, e.g. glycol, or alcohols with other functional groups,

such as ethanolamine or glycol ethers.

The amides according to the invention derived from the carboxylic acids of general formula I are preferably prepared according to per se known methods from the carboxylic acids or their reactive derivatives (such as e.g. carboxylic acid halides, esters, azides, anhydrides or mixed anhydrides) by reaction with amines. As amino components, there come into question e.g. ammonia, alkylamines, dialkylamines but also amino-alcohols, such as e.g. ethanolamine and 2-aminopropanol, as well as amino acids, such as e.g. p-aminobenzoic acid, β-alanine and others. Other valuable amine components are alkyl, aralkyl and arylpiperazines.

For the preparation of salts with pharmacologically acceptable organic or inorganic bases, such as e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide, ammonium hydroxide, methylglucamine, morpholine or ethanolamine, the carboxylic acids can be reacted with the corresponding bases. Mixtures of the carboxylic acids with a suitable alkali metal carbonate or hydrogen carbonate also come into consideration.

The new compounds of the general formula I and their physiologically acceptable salts, as well as their esters and amides, show not only an excellent lipid-sinking action but also an outstanding inhibiting action on the thrombocyte aggregation.

For the preparation of medicaments, the compounds of the general formula I are mixed in per se known manner with suitable pharmaceutical carrier substances, aroma, flavouring and colouring materials and formed, for example, as tablets or dragees or, with the addition of corresponding adjuvants, suspended or dissolved in water or oil, such as e.g. olive oil.

The substances of the general formula I can be administered orally and parenterally in liquid or solid form. As injection medium, water is preferably used which contains the stabilising agents, solubilising agents and/or buffers usual in the case of injection solutions. Such additives are e.g. tartrate or borate buffers, ethanol, dimethyl sulphoxide, complex formers (such as ethylenediamine-tetraacetic acid), high molecular polymers (such as liquid polyethylene oxide) for viscosity regulation or polyethylene derivatives of sorbitan anhydrides.

Solid carrier materials are e.g. starch, lactose, mannitol, methyl cellulose, talc, highly dispersed silicic acid, high molecular fatty acids (such as stearic acid), gelatine, agar-agar, calcium phosphate, magnesium stearate, animal and vegetable fats or solid high molecular polymers (such as polyethylene glycols). Compositions suitable for oral administration can, if desired, contain flavouring and sweetening materials.

The dosage administered depends upon the age, state of health and the weight of the recipient, the extent of the disease, the nature of simultaneously possibly carried out further treatments, the frequency of the treatments and the nature of the desired action. Usually, the daily dosage of the active compound amounts to 0.1 to 50 mg./kg. of body weight. Normally, 0.5 to 40 and preferably 1.0 to 20 mg./kg./day in one or more applications per day are effective in order to obtain the desired results.

The superior action of the compounds according to the invention in comparison with the commercial preparation acetylsalicylic acid is shown on the basis of the following experiments:

Experimental protocol

1. Lipid sinking

The substance to be tested was administered p.o., in each case, to 10 male, metabolically healthy rats for 7 days in a dosage of 50 mg./kg. in methyl cellulose suspension. At the end of the experiment, 3 hours after the last probe administration, the cholesterol and triglyceride values in the serum were determined. The changes were determined in comparison with control collectives.

2. Aggregation inhibition

The influencing of the thrombocyte aggregation was carried out according to the Born test:

a) Method

Venous blood from metabolically healthy subjects is mixed with sodium citrate (9:1). The erythrocytes were sedimented by centrifuging at 150 g. The thrombocytes are enriched in the supernatant. This supernatant is referred to as platelet-rich plasma (PRP).

An aliquot of the PRP is introduced into the cuvette of an aggregometer (Universal Aggregometer of the firm Braun, Melsungen) and there stirred by means of a small magnet. The substance to be tested is added in an aqueous solution (pH about 7). Changes of the light transmission in the suspension are continuously recorded by a recorder.

After expiry of the spontaneous aggregation, an aggregation is initiated by the addition of 5×10^{-6} M adrenaline. Comparatively large thrombocyte aggregates are formed and the light transmission through the suspension thereby increases.

b) Evaluation

The adrenaline-induced aggregation takes place in 2 phases, i.e. the light transmission first increases, then stagnates for a short time and again increases. Only the 2nd phase of the aggregation can be influenced by aggregation inhibitors.

For the documentation of the results, the angle of the 2nd aggregation phase is determined against the horizontals for the aggregation induced by adrenaline

and this is taken as 0% inhibition (control experiment).

With the same PRP, after addition of the test substance, the aggregation is induced with adrenaline and the course of the aggregation recorded via the recorder. The angle of the 2nd phase with regard to the horizontals is again determined and the ratio of the two angles gives the % inhibition of the 2nd phase of the thrombocyte aggregation.

For the comparison preparation acetylsalicylic acid, the inhibition at a concentration of 10^{-4} M amounts to 100%. At a concentration of 5×10^{-5} M 0%.

All substances are tested at the aggregation of 5×10^{-5}M.

substance from Example	lipid sinking Triglycerides (%)	lipid sinking Cholesterol (%)	inhibition of the adrenaline-induced aggregation (at 5×10^{-5} M)
1	24	7	0
1a	9	13	100
1b	0	10	0
1c	38	7	100
1d	10	10	0
3	34	8	100
3a	0	20	0
3b	10	3	0
3c	30	7	50
3f	24	5	100
3g	20	10	30
4	10	10	100
4a	31	11	100
4b, 7	39	16	20
4c	0	12	0
4d, 6	42	19	100
4e	20	6	100
4f	14	0	100
4g	10	0	100
4h	22	0	50
4i	27	0	100
4k	50	25	50
4 l	20	0	100
4m	22	12	100

(61)

Preferred in the meaning of the invention are, apart from the compounds mentioned in the Examples and the compounds derivable by combination of all meanings of the substituents mentioned in the claims, also in particular the following compounds:

4-(2-benzenesulphonamidoethyl)-phenylacetamide

3-{4-[2-(4-phenylsulphonamido)-ethyl]-phenyl}-propionic acid

3-{4-[2-(4-phenylsulphonamido)-ethyl]-phenyl}-propionamide

3-{4-[2-(4-phenylsulphonamido)-ethyl]-phenyl}-propionic acid ethyl ester.

The following Examples show some of the numerous process variants which can be used for the synthesis of the compounds according to the invention. However, they do not represent a limitation of the subject matter of the invention.

Example 1

4-[2-(2-Phenylethanesulphonamido)-ethyl]-benzoic acid

To an ice-cooled solution of 14.3 g. (70 mmole) 4-(2-aminoethyl)-benzoic acid ethyl ester hydrochloride in 150 ml. abs. pyridine are added dropwise, in the course of one hour, while stirring, 16.1 g. (70 mmole) 2-phenylethanesulphochloride. One then removes the cooling bath and stirs for 2 hours at room temperature. Subsequently, one pours into water and acidifies with concentrated hydrochloric acid, whereby an oil separates

out which is taken up in ether. One further extracts the aqueous phase several times with ether, dries the combined ether phases with sodium sulphate and finally evaporates. One recrystallises the residue from a mixture of ethyl acetate and ligroin. There remain 18.4 g. (73% of theory) 4-[2-(2-phenylethanesulphonamido)-ethyl]-benzoic acid ethyl ester with the m.p. 83-86°C.

One maintains a mixture of 12.5 g. (35 mmole) 4-[2-(2-phenylethanesulphonamido)-ethyl]-benzoic acid ethyl ester, 70 ml. 1N aqueous potassium hydroxide solution and 200 ml. methanol for 2 hours at 35°C. It is then acidified with 2N hydrochloric acid. One evaporates off the methanol and extracts the remaining aqueous phase several times with methylene chloride. The combined methylene chloride phases are washed with water, dried over sodium sulphate and evaporated. One dissolves the evaporation residue in sodium hydrogen carbonate solution and precipitates out by the addition of 5N hydrochloric acid. The crystals are filtered off with suction and dried. There result 9.3 g. (88% of theory) 4-[2-(2-phenylethanesulphonamido)-ethyl]-benzoic acid with the m.p. 183-186°C.

In analogy thereto, one obtains

a) 4-[2-(4-chlorobenzenesulphonamido)-ethyl]-benzoic acid ethyl ester

from 4-(2-aminoethyl)-benzoic acid ethyl ester hydro-

chloride and 4-chlorobenzenesulphochloride
m.p. 87-89°C.; yield 84% of theory,
and therefrom by hydrolysis
4-[2-(4-chlorobenzenesulphonamido)-ethyl]-benzoic acid
m.p. 199-201°C.; yield 91% of theory.

b) 4-{2-[2-(4-chlorophenyl)-ethanesulphonamido]-ethyl}-phenylacetic acid ethyl ester
from 4-(2-aminoethyl)-phenylacetic acid ethyl ester hydrochloride and 2-(4-chlorophenyl)-ethanesulpho-chloride
m.p. 69-70°C. (aqueous ethanol); yield 76% of theory
and therefrom by hydrolysis
4-{2-[2-(4-chlorophenyl)-ethanesulphonamido]-ethyl}-phenylacetic acid
m.p. 155-156°C. (aqueous ethanol); yield 67% of theory.

c) 4-{2-[2-(4-chlorophenyl)-ethenesulphonamido]-ethyl}-phenylacetic acid ethyl ester
from 4-(2-aminoethyl)-phenylacetic acid ethyl ester hydrochloride and 2-(4-chlorophenyl)-ethanesulpho-chloride
m.p. 101-102°C. (66% ethanol); yield 70% of theory,
and therefrom by hydrolysis
4-{2-[2-(4-chlorophenyl)-ethenesulphonamido]-ethyl}-phenylacetic acid
m.p. 175-176°C. (aqueous ethanol); yield 87% of theory.

d) 4-[2-(4-chlorobenzenesulphonamido)-ethyl]-phenyl-acetic acid ethyl ester

from 4-(2-aminoethyl)-phenylacetic acid ethyl ester hydrochloride and 4-chlorobenzenesulphochloride m.p. 88-90°C. (ethyl acetate + ligroin); yield 96% of theory,

and therefrom by hydrolysis 4-[2-(4-chlorobenzenesulphonamido)-ethyl]-phenylacetic acid m.p. 138-140°C. (ethyl acetate + ligroin); yield 93% of theory.

Example 2

4-(2-Methanesulphonamidoethyl)-benzoic acid

Into a mixture of 150 ml. abs. pyridine, 12.8 g. (92 mmole) pulverised, anhydrous potassium carbonate and 21.25 g. (92 mmole) 4-(2-aminoethyl)-benzoic acid ethyl ester hydrochloride one adds dropwise at 10 - 15°C. 10.6 g. (92 mmole) methanesulphochloride. Subsequently, it is stirred for 30 minutes at 20°C., then 5 minutes at 80°C., thereafter cooled and poured into ice water. One acidifies with concentrated hydrochloric acid and extracts the precipitated substance with methylene chloride. After drying over sodium sulphate, the methylene chloride phase is evaporated. One thus obtains 24.8 g. (98% of theory) 4-(2-methanesulphonamidoethyl)-benzoic acid ethyl ester, m.p. 96-99°C.

By hydrolysis of the ethyl ester in analogy to Example 1, one obtains 93% of theory of 4-(2-methanesulphonamidoethyl)-benzoic acid with the m.p. 173-174°C.

In analogy thereto, one obtains

a) 4-(2-methanesulphonamidoethyl)-phenylacetic acid ethyl ester

from 4-(2-aminoethyl)-phenylacetic acid ethyl ester hydrochloride and methanesulphochloride

colourless oil; yield 81% of theory

and therefrom by hydrolysis

4-(2-methanesulphonamidoethyl)-phenylacetic acid

m.p. 170-172°C. (ethyl acetate + ethanol); yield 79% of theory.

b) 2-{4-[2-(2-phenylethanesulphonamido)-ethyl]-phenyl}-propionic acid ethyl ester

from 2-[4-(2-aminoethyl)-phenyl]-propionic acid ethyl ester hydrochloride and 2-phenylethanesulphochloride

colourless oil; yield 77% of theory

and therefrom by hydrolysis

2-{4-[2-(2-phenylethanesulphonamido)-ethyl]-phenyl}-propionic acid

m.p. 94-97°C. (ether + ligroin); yield 60% of theory.

c) 2-{4-[2-(2-phenylethanesulphonamido)-ethyl]-phenyl}-2-methylpropionic acid ethyl ester

from 2-[4-(2-aminoethyl)-phenyl]-2-methylpropionic acid ethyl ester hydrochloride and 2-phenylethanesulphochloride

colourless oil; yield 52% of theory,

and therefrom by hydrolysis

2-{4-[2-(2-phenylethanesulphonamido)-ethyl]-phenyl}-2-

methylpropionic acid

m.p. 109-110°C. (ethanol + water); yield 62% of theory.

d) 3-<4-{2-[2-(4-chlorophenyl)-ethanesulphonamido]-ethyl}-phenyl>-propionic acid ethyl ester

from 3-[4-(2-aminoethyl)-phenyl]-propionic acid ethyl ester hydrochloride and 2-(4-chlorophenyl)-ethanesulphochloride

m.p. 70-71°C. (ethanol); yield 66% of theory,

and therefrom by hydrolysis

3-<4-{2-[2-(4-chlorophenyl)-ethanesulphonamido]-ethyl}-phenyl>-propionic acid

m.p. 157-158°C. (ethanol + water); yield 76% of theory.

e) 3-{4-[2-(4-chlorobenzenesulphonamido)-ethyl]-phenyl}-propionic acid ethyl ester

from 3-[4-(2-aminoethyl)-phenyl]-propionic acid ethyl ester hydrochloride and 4-chlorobenzenesulphochloride

m.p. 61-62°C. (ethanol); yield 65% of theory,

and therefrom by hydrolysis

3-{4-[2-(4-chlorobenzenesulphonamido)-ethyl]-phenyl}-propionic acid

m.p. 129-130°C. (ethanol + water); yield 87% of theory.

f) 4-[2-(2-phenylethanesulphonamido)-ethyl]-cinnamic acid ethyl ester

from 4-(2-aminoethyl)-cinnamic acid ethyl ester hydrochloride and 2-phenylethanesulphochloride

m.p. 98-99°C.; yield 77% of theory,

and therefrom by hydrolysis

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4-[2-(2-phenylethanesulphonamido)-ethyl]-cinnamic acid
m.p. 187-188°C.; yield 76% of theory.

g) 4-{2-[2-(4-chlorophenyl)-ethanesulphonamido]-ethyl}-cinnamic acid ethyl ester

from 4-(2-aminoethyl)-cinnamic acid ethyl ester hydrochloride and 2-(4-chlorophenyl)-ethanesulphochloride
m.p. 91-92°C. (ethanol + water); yield 63% of theory
and therefrom by hydrolysis
4-{2-[2-(4-chlorophenyl)-ethanesulphonamido]-ethyl}-cinnamic acid
m.p. 212-213°C. (ethanol + water); yield 94% of theory.

h) 4-[2-(4-chlorobenzenesulphonamido)-ethyl]-cinnamic acid ethyl ester

from 4-(2-aminoethyl)-cinnamic acid ethyl ester hydrochloride and 4-chlorobenzenesulphochloride
m.p. 97-98°C. (ethanol); yield 92% of theory,
and therefrom by hydrolysis
4-[2-(4-chlorobenzenesulphonamido)-ethyl]-cinnamic acid
m.p. 173-175°C.; yield 93% of theory.

i) 4-[2-(1-naphthylsulphonamido)-ethyl]-cinnamic acid ethyl ester

from 4-(2-aminoethyl)-cinnamic acid ethyl ester hydrochloride and 1-naphthylsulphochloride
m.p. 85-86°C. (ethanol); yield 88% of theory,
and therefrom by hydrolysis
4-[2-(1-naphthylsulphonamido)-ethyl]-cinnamic acid
m.p. 175°C. (ethanol + water); yield 93% of theory.

j) 4-[2-(2-phenylethenesulphonamido)-ethyl]-cinnamic acid ethyl ester

from 4-(2-aminoethyl)-cinnamic acid ethyl ester hydrochloride and 2-phenylethenesulphochloride

m.p. 102-104°C.; yield 63% of theory,

and therefrom by hydrolysis

4-[2-(2-phenylethenesulphonamido)-ethyl]-cinnamic acid

m.p. 190-191°C.; yield 94% of theory.

k) 4-{2-[2-(4-chlorophenyl)-ethenesulphonamido)-ethyl}-cinnamic acid ethyl ester

from 4-(2-aminoethyl)-cinnamic acid ethyl ester hydrochloride and 2-(4-chlorophenyl)-ethenesulphochloride

m.p. 131-132°C. (ethanol); yield 83% of theory,

and therefrom by hydrolysis

4-{2-[2-(4-chlorophenyl)-ethenesulphonamido]-ethyl}-cinnamic acid

m.p. 211-212°C. (ethanol + water); yield 78% of theory.

Example 3

4-[2-(4-Toluenesulphonamido)-ethyl]-phenylacetic acid

To a solution of 14.6 g. (60 mmole) 4-(2-aminoethyl)-phenylacetic acid ethyl ester hydrochloride in 120 ml. abs. pyridine one adds dropwise at 0 - 10°C. in 5 minutes a mixture of 12.0 g. (63 mmole) 4-toluenesulphochloride and 50 ml. pyridine, allows to come to room temperature and then keeps for 45 minutes at 60°C. One subsequently evaporates in a vacuum to half the volume, pours into water and acidifies with hydrochloric

acid. The precipitates viscous mass is taken up in ethyl acetate and the solution dried over sodium sulphate. One evaporates in a vacuum and recrystallises the residue from a mixture of ethyl acetate and ligroin. One thus obtains 18.0 g. (82% of theory) 4-[2-(4-toluenesulphonamido)-ethyl]-phenylacetic acid ethyl ester with the m.p. 113 - 115°C.

To a solution of 13.3 g. (37 mmole) 4-[2-(4-toluenesulphonamido)-ethyl]-phenylacetic acid ethyl ester in 220 ml. ethanol one adds dropwise 110 ml. 1N aqueous potassium hydroxide solution and subsequently keeps for 2 hours at 35 - 40°C. The ethanol is then distilled off in a vacuum and the aqueous phase extracted with ether. Addition of 55 ml. 2N hydrochloric acid leads to the separation of a colourless precipitate which is filtered off with suction and recrystallised from a mixture of ethyl acetate and ligroin. Yield 10.8 g. (88% of theory) 4-[2-(4-toluenesulphonamido)-ethyl]-phenylacetic acid with the m.p. 141 - 143°C.

In analogy thereto, one obtains

a) 4-[2-(2-phenylethenesulphonamido)-ethyl]-benzoic acid ethyl ester

from 4-(2-aminoethyl)-benzoic acid ethyl ester hydrochloride and 2-phenylethenesulphochloride

m.p. 59-61°C. (ethanol + water); yield 66% of theory, and therefrom by hydrolysis

4-[2-(2-phenylethenesulphonamido)-ethyl]-benzoic acid

m.p. 169.5 - 170°C. (ethyl acetate); yield 81% of theory.

b) 4-[2-(2-phenylethanesulphonamido)-ethyl]-phenyl-acetic acid ethyl ester

from 4-(2-aminoethyl)-phenylacetic acid ethyl ester hydrochloride and 2-phenylethanesulphochloride

colourless oil; yield 61% of theory,

and therefrom by hydrolysis

4-[2-(2-phenylethanesulphonamido)-ethyl]-phenylacetic acid

m.p. 150 - 152°C. (ethyl acetate); yield 69% of theory.

c) 4-[2-(2-phenylethanesulphonamido)-ethyl]-phenylacetic acid ethyl ester

from 4-(2-aminoethyl)-phenylacetic acid ethyl ester hydrochloride and 2-phenylethenesulphochloride

colourless oil; yield 78% of theory,

and therefrom by hydrolysis

4-[2-(2-phenylethenesulphonamido)-ethyl]-phenylacetic acid

m.p. 146 - 149°C. (ethyl acetate + ligroin); yield 81% of theory.

d) 3-{4-[2-(2-chlorobenzenesulphonamido)-ethyl]-phenyl}-propionic acid ethyl ester

from 3-[4-(2-aminoethyl)-phenyl]-propionic acid ethyl ester hydrochloride and 2-chlorobenzenesulphochloride

m.p. 57 - 60°C.; yield 94% of theory,

and therefrom by hydrolysis

3-{4-[2-(2-chlorobenzenesulphonamido)-ethyl]-phenyl}-propionic acid

m.p. 136 - 139°C. (ethyl acetate + ligroin); yield 82% of theory.

e) 3-{4-[2-(3-methoxybenzenesulphonamido)-ethyl]-phenyl}-propionic acid ethyl ester

from 3-[4-(2-aminoethyl)-phenyl]-propionic acid ethyl ester hydrochloride and 3-methoxybenzenesulphochloride

colourless oil; yield 92% of theory,

and therefrom by hydrolysis

3-{4-[2-(3-methoxybenzenesulphonamido)-ethyl]-phenyl}-propionic acid

m.p. 100 - 103°C. (triturated with ether); yield 65% of theory.

f) 3-{4-[2-(3-trifluoromethylbenzenesulphonamido)-ethyl]-phenyl}-propionic acid ethyl ester

from 3-[4-(2-aminoethyl)-phenyl]-propionic acid ethyl ester hydrochloride and 3-trifluoromethylbenzenesulphochloride

colourless oil; yield 99% of theory,

and therefrom by hydrolysis

3-{4-[2-(3-trifluoromethylbenzenesulphonamido)-ethyl]-phenoxy}-propionic acid

m.p. 119 - 121°C. (toluene); yield 74% of theory.

g) 3-<4-{2-[2-(4-chlorophenyl)-ethenesulphonamido]-ethyl}-phenyl>-propionic acid ethyl ester

from 3-[4-(2-aminoethyl)-phenyl]-propionic acid ethyl

ester hydrochloride and 2-(4-chlorophenyl)-ethene-sulphonyl chloride

m.p. 94 - 96°C. (ethyl acetate + ligroin); yield 86% of theory,

and therefrom by hydrolysis

3-<4-{2-[2-(4-chlorophenyl)-ethenesulphonamido]-ethyl}-phenyl>-propionic acid

m.p. 165°C. (ethyl acetate + methanol); yield 73% of theory.

Example 4

4-[2-(4-Fluorobenzenesulphonamido)-ethyl]-phenylacetic acid

One heats a mixture of 11.0 g. (51 mmole) 4-(2-aminoethyl)-phenylacetic acid hydrochloride, 8.3 g. (60 mmole) potassium carbonate and 200 ml. water to 80°C. and, at this temperature, adds thereto 9.5 g. (49 mmole) 4-fluorobenzenesulphochloride. Thereafter, it is maintained for a further 2 hours at 80°C., then cooled and brought to pH 2 by means of 2N hydrochloric acid. One filters off with suction the precipitated deposit, dries it and recrystallises it from 66% ethanol. One obtains 10.2 g. (62% of theory) 4-[2-(4-fluorobenzenesulphonamido)-ethyl]-phenylacetic acid with the m.p. 121 - 122°C.

In analogy thereto, one obtains

a) 3-[4-(2-benzenesulphonamidoethyl)-phenyl]-propionic acid

from 3-[4-(2-aminoethyl)-phenyl]-propionic acid hydrochloride and benzenesulphochloride

m.p. 102.5 - 103°C. (ethyl acetate + ligroin); yield 63% of theory.

b) 4-(2-benzenesulphonamidoethyl)-benzoic acid

from 4-(2-aminoethyl)-benzoic acid hydrochloride and benzenesulphochloride

m.p. 144.5 - 145°C. (aqueous ethanol); yield 74% of theory.

c) 4-[2-(4-methoxybenzenesulphonamido)-ethyl]-benzoic acid

from 4-(2-aminoethyl)-benzoic acid hydrochloride and 4-methoxybenzenesulphochloride

m.p. 177 - 178°C. (aqueous ethanol); yield 68% of theory.

d) 4-(2-benzenesulphonamidoethyl)-phenylacetic acid

from 4-(2-aminoethyl)-phenylacetic acid hydrochloride and benzenesulphochloride

m.p. 127 - 128°C. (ligroin + isopropanol); yield 92% of theory.

e) 4-[2-(4-methoxybenzenesulphonamido)-ethyl]-phenylacetic acid

from 4-(2-aminoethyl)-phenylacetic acid hydrochloride and 4-methoxybenzenesulphochloride

m.p. 160 - 162°C. (aqueous ethanol); yield 72% of theory.

f) 4-[2-(4-acetylbenzenesulphonamide)-ethyl]-phenyl-acetic acid

from 4-(2-aminoethyl)-phenylacetic acid hydrochloride and 4-acetylbenzenesulphochloride

m.p. 193 - 194°C. (aqueous ethanol); yield 82% of theory.

g) 4-[2-(2-naphthalenesulphonamido)-ethyl]-phenylacetic acid

from 4-(2-aminoethyl)-phenylacetic acid hydrochloride and 2-naphthalenesulphochloride

m.p. 135 - 136°C. (aqueous ethanol); yield 68% of theory.

h) 4-(2-benzenesulphonamidoethyl)-cinnamic acid

from 4-(2-aminoethyl)-cinnamic acid hydrochloride and benzenesulphochloride

m.p. 164 - 166°C. (aqueous ethanol); yield 73% of theory.

i) 4-(3-benzenesulphonamidopropyl)-benzoic acid

from 4-(3-aminopropyl)-benzoic acid hydrochloride and benzenesulphochloride

m.p. 207.5 - 209°C. (acetone + water); yield 63% of theory.

j) 4-(3-benzenesulphonamidopropyl)-phenylacetic acid

from 4-(3-aminopropyl)-phenylacetic acid hydrochloride and benzenesulphochloride

m.p. 128 - 129°C. (ethyl acetate + ligroin); yield 84% of theory.

k) 2-[4-(2-benzenesulphonamidoethyl)-phenyl]-2-methyl-propionic acid

from 2-[4-(2-aminoethyl)-phenyl]-2-methylpropionic acid hydrochloride and benzenesulphochloride

m.p. 86 - 88°C. (ethyl acetate); yield 80% of theory.

l) 4-[2-(2,5-dichlorobenzenesulphonamido)-ethyl]-phenylacetic acid

from 3-[4-(2-aminoethyl)-phenyl]-acetic acid hydrochloride and 2,5-dichlorobenzenesulphochloride

m.p. 163 - 164°C. (aqueous ethanol); yield 65% of theory.

m) 4-[4-(2-benzenesulphonamidoethyl)-phenyl]-butyric acid

from 4-[4-(2-aminoethyl)-phenyl]-butyric acid hydrochloride and benzenesulphochloride

m.p. 70 - 71°C. (aqueous ethanol); yield 67% of theory.

n) 2-[4-(2-benzenesulphonamidoethyl)-phenyl]-propionic acid

from 2-[4-(2-aminoethyl)-phenyl]-propionic acid hydrochloride and benzenesulphochloride

m.p. (sodium salt) 236 - 239°C.; yield 83% of theory.

o) 3-[4-(2-benzenesulphonamidoethyl)-phenyl]-2-methyl-propionic acid

from 3-[4-(2-aminoethyl)-phenyl]-2-methylpropionic acid hydrochloride and benzenesulphochloride

m.p. 113 - 115°C. (ethyl acetate + ligroin); yield 85% of theory.

p) 4-(2-benzenesulphonamidoethyl)-α-methylcinnamic acid from 4-(2-aminoethyl)-α-methylcinnamic acid hydrochloride and benzenesulphochloride

m.p. 147 - 148°C.; yield 62% of theory.

q) 4-[2-(2-naphthylsulphonamido)-ethyl]-cinnamic acid from 4-(2-aminoethyl)-cinnamic acid hydrochloride and 2-naphthylsulphochloride

m.p. 192 - 193°C. (ethanol + water); yield 96% of theory.

Example 5

4-[2-(N-Methylbenzenesulphonamido)-ethyl]-phenylacetic acid

To a mixture of 10.4 g. (30 mmole) 4-(2-benzenesulphonamidoethyl)-phenylacetic acid ethyl ester (prepared by esterification of the acid according to Example 4 d with ethanol; m.p. 58 - 60°C.), 60 ml. hexamethylphosphoric acid triamide and 60 ml. abs. toluene one adds 0.72 g. (30 mmole) sodium hydride (as mineral oil suspension) and subsequently stirs for 2 hours at 80°C. It is then cooled, mixed with a mixture of 12.8 g. (90 mmole) methyl iodide and 12 ml. hexamethylphosphoric acid triamide, stirred for 15 minutes at 20°C. and then kept for 3 hours at 80°C. After cooling, one pours on to ice, brings to pH 3 by means of hydrochloric acid and extracts several times by means of toluene. The toluene phase is evaporated, the evaporation residue chromatographed by means of silica

gel/toluene. One obtains 5.1 g. (47% of theory) pure 4-[2-(N-methylbenzenesulphonamido)-ethyl]-phenylacetic acid ethyl ester as colourless oil with the refractive index n_D^{20} = 1.5590.

From this one obtains by hydrolysis by means of 1N potassium hydroxide solution in ethanol:
4-[2-(N-methylbenzenesulphonamido)-ethyl]-phenylacetic acid
m.p. 159 - 160°C. (ethyl acetate); yield 63% of theory.

Example 6

Δ-(2-Benzenesulphonamidoethyl)-phenylacetic acid

To an ice-cooled mixture of 52.3 g. (0.2 mole) N-(2-phenylethyl)-benzenesulphonamide, 80 ml. 1,1,2,2-tetrachloroethane and 40.8 g. (0.52 mole) acetyl chloride are added portionwise, with stirring, 88 g. (0.664 mole) aluminium trichloride. The addition is finished after 1.5 hours. One leaves the reaction mixture for 45 minutes at 0°C. and then gradually heats to 80°C. After 1.5 hours, one pours on to ice and separates off the organic phase. The aqueous portion is extracted with methylene chloride, the combined organic phases dried over sodium sulphate and evaporated. The residue is heated to reflux temperature, while stirring, with 1 litre 2N aqueous sodium hydroxide solution. After cooling, one extracts with methylene chloride, dries the organic phase over sodium sulphate and evaporates. One triturates the residue with ether and filters off

the crystals with suction. One obtains 31.3 g. (52% of theory) 4-(2-benzenesulphonamidoethyl)-acetophenone, m.p. 133 - 135°C.

A mixture of 9.4 g. (31 mmole) 4-(2-benzenesulphonamidoethyl)-acetophenone, 1.6 g. (50 mmole) sulphur and 20 ml. morpholine are heated, while stirring, for 19 hours to 135°C. After cooling, the reaction mixture is poured into water and the aqueous phase extracted with methylene chloride. One washes the methylene chloride phase with 1N hydrochloric acid, dries it over sodium sulphate and evaporates. The evaporation residue is taken up in 100 ml. 1N aqueous sodium hydroxide solution and the solution heated to the boiling temperature for 2 hours. One extracts the cooled reaction mixture with ethyl acetate and, by the addition of hydrochloric acid, precipitates from the aqueous phase the 4-(2-benzenesulphonamidoethyl)-phenylacetic acid which, in all physical properties, is identical to the substances mentioned under Example 4 d; yield 56% of theory.

Example 7

Δ-(2-Benzenesulphonamidoethyl)-benzoic acid

One dissolves 11.0 g. (0.28 mole) caustic soda in 90 ml. water, adds 66 ml. dioxan thereto and mixes the mixture dropwise, while stirring, with 16 g. (0.1 mole) bromine. One then cools in an ice-bath with further stirring and adds thereto 10 g. (0.033 mole)

4-(2-benzenesulphonamidoethyl)-acetophenone. After 2 hours, the carboxylic acid is precipitated out by the addition of hydrochloric acid. One recrystallises from aqueous ethanol and obtains 8.2 g. (81% of theory) 4-(2-benzenesulphonamidoethyl)-benzoic acid which, in all physical properties, is identical to the substance mentioned under Example 4 b.

Example 8

4-(2-Benzenesulphonamidoethyl)-phenylacetic acid (4-methylpiperazide)

One heats a mixture of 16.0 g. (0.05 mole) 4-(2-benzenesulphonamidoethyl)-phenylacetic acid, 100 ml. benzene and 17.9 g. (0.15 mole) thionyl chloride for 5 hours to reflux temperature. Benzene and excess thionyl chloride are then distilled off in a vacuum. Crude yield: quantitative. After recrystallisation from toluene, one obtains 14.9 g. (88% of theory) 4-(2-benzenesulphonamidoethyl)-phenylacetyl chloride; m.p. 82°C. (decomp.).

To an ice-cooled solution of 3.0 g. (30 mmole) N-methylpiperazine and 100 ml. abs. pyridine are added portionwise in the course of an hour, while stirring, 10.1 g. (30 mmole) 4-(2-benzenesulphonamidoethyl)-phenylacetyl chloride. Subsequently, one allows the temperature to come to 20°C., heats to 90°C. for 5 hours, cools and pours into about 500 ml. ice water. The mixture is extracted with methylene chloride and

the methylene chloride phase, after drying over sodium sulphate, evaporated. One takes up the residue in ether and precipitates the hydrochloride with ethereal hydrochloric acid. After recrystallisation from ethanol, one obtains 8.7 g. (66% of theory) 4-(2-benzenesulphonamidoethyl)-phenylacetic acid (4-methyl-piperazide) hydrochloride; m.p. 168°C.

Example 9

4-[2-(4-Hydroxyphenylsulphonamido)-ethyl]-phenylacetic acid

One mixes a mixture of 8.75 g. (36 mmole) 4-(2-aminoethyl)-phenylacetic acid ethyl ester and 90 ml. methylene chloride with 7.3 g. (72 mmole) triethylamine and first stirs the mixture for 1 hour at room temperature. One then cools in an ice-bath and slowly adds dropwise thereto a solution of 9.5 g. (36 mmole) 4-ethoxycarbonyloxybenzenesulphochloride in 10 ml. methylene chloride. The reaction mixture is left for 1 hour at 0°C., then for 3 hours at room temperature. Subsequently, one washes the organic phase with dilute hydrochloric acid and water, dries and evaporates.

As residue, one obtains 15.0 g. (96% of theory) 4-[2-(4-ethoxycarbonyloxyphenylsulphonamido)-ethyl]-phenylacetic acid ethyl ester, colourless oil.

14.8 g. (34 mmole) of the crude ester are heated to reflux temperature with 100 ml. 2N aqueous sodium hydroxide solution. After cooling, one clarifies the

now resulting solution with active charcoal and precipitates out with hydrochloric acid the 4-[2-(4-hydroxyphenylsulphonamido)-ethyl]-phenylacetic acid. M.p. 157 - 159°C. (ethyl acetate + toluene); yield 67% of theory.

Example 10

Tablets were prepared: each tablet contains 10 mg. 3-[4-(2-benzenesulphonamidoethyl)-phenyl]-propionic acid. The tablets were produced according to the following recipe:

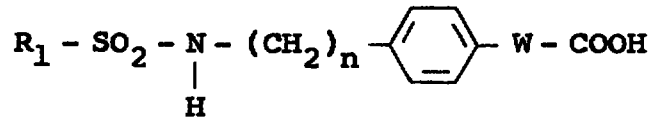
3-[4-(2-benzenesulphonamidoethyl)-phenyl]-propionic acid	10 g.
lactose	80 g.
starch	29 g.
magnesium stearate	1 g.

The above compound was finely pulverised and mixed with lactose and starch. The mixture was granulated in the usual way. Magnesium stearate was added to the granulate and the mixture pressed into 1000 tablets with an individual weight of 0.12 g.

* C L M S *

CLAIMS

1. Sulphonamides of the general formula (I)



(I)

in which R_1 signifies an aryl, aralkyl or aralkenyl group, wherein the alkyl radical of the aralkyl group contains 1 - 5 C-atoms and the alkenyl radical of the aralkenyl group contains 2 - 3 C-atoms and whereby the aryl radical means, in each case, an aromatic hydrocarbon with 6 - 12 C-atoms, which can optionally be substituted one or more times by hydroxyl, halogen, trifluoromethyl, lower alkyl or lower alkoxy with 1 - 5 C-atoms or acetyl, n signifies the numbers 2 and 3, W represents a bond or an unbranched or branched alkylene chain with 1 - 4 C-atoms, which is either saturated or contains a double bond; as well as their physiologically acceptable salts, esters and amides.

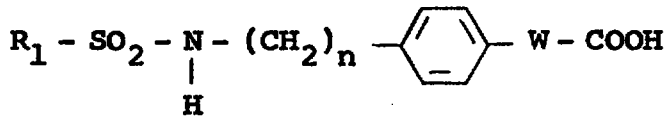
2. Compounds according to claim 1, characterised in that R_1 and W have the given meanings and n signifies the number 2.

3. Compounds according to one of claims 1 or 2, characterised in that R_1 and n have the given meanings and W signifies a bond.

4. Compounds according to one of claims 1 and 2, characterised in that R_1 and n have the given meanings and W signifies one of the groups $-CH_2-$, $-CH_2CH_2-$ or $-C(CH_3)_2-$.

5. Compounds according to claim 4, characterised in that n and W have the given meanings and R_1 signifies a phenyl radical optionally substituted once or more times by chlorine, fluorine, trifluoromethyl or methoxy.

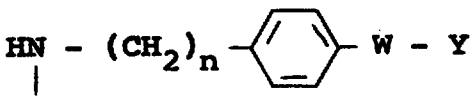
6. Process for the preparation of sulphonamides of the general formula I



(I)

in which R_1 signifies an aryl, aralkyl or aralkenyl group, wherein the alkyl radical of the aralkyl group contains 1 - 5 C-atoms and the alkenyl radical of the aralkenyl group contains 2 - 3 C-atoms and whereby the aryl radical means, in each case, an aromatic hydrocarbon with 6 - 12 C-atoms, which can optionally be substituted one or more times by hydroxyl, halogen, trifluoromethyl, lower alkyl or lower alkoxy with 1 - 5 C-atoms or acetyl, n signifies the numbers 2 and 3, W represents a bond or an unbranched or branched alkylene chain with 1 - 4 C-atoms which is either saturated or contains a double bond, as well as of their physiologically acceptable salts, esters and amides thereof; characterised in that one

a) reacts an amine of the general formula II



(II)

in which

n and W have the above-given meaning and

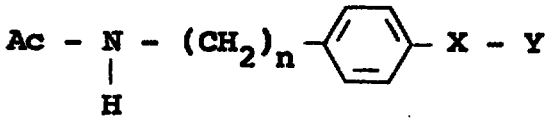
Y represents a $-COOR_2$ group, in which R_2 signifies a hydrogen atom or a lower alkyl group, an acid amide group or a residue which, after condensation has taken place, is converted into the $COOR_2$ group or into an acid amide group, in per se known manner with a sulphonic acid of the general formula III

$$R_1 - SO_2OH \qquad \text{(III)}$$

in which

R_1 has the above-given meaning,

or with a derivative thereof or, instead of the free amine of the general formula II uses its salts; or - as a variant of this process - carries out a trans-acylation which then takes place when one reacts a free sulphonic acid III with a compound of the general formula IV



(IV)

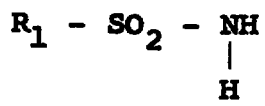
in which

n, Y and W have the above-given meaning and

Ac represents an easily exchangeable acyl radical, in a suitable solvent;

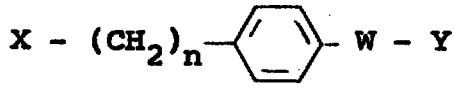
or

b) reacts a sulphonamide of the general formula V



(V)

in which R_1 has the above-given meaning, with a compound of the general formula VI



(VI)

in which

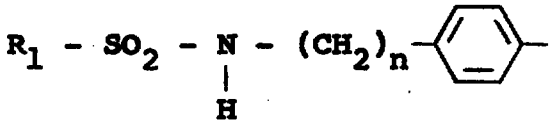
n and W have the above-given meaning,

Y represents a $-COOR_2$ group, in which R_2 signifies a hydrogen atom or a lower alkyl group, an acid amide group or a residue which, after condensation has taken place, is converted into the $COOR_2$ group or into an acid amide group and

X is to represent a reactive group; subsequent to the reactions having taken place optionally converts the acid derivative obtained of general formula I into an ester, into an amide or into a physiologically acceptable salt;

or

c) oxidises a compound of general formula VII



(VII)

in which

R_1, n and W have the above-given meaning and

Z represents a residue oxidatively convertible into the carboxyl group.

7. Compounds of formula I according to claim 1 for the achievement of a thrombocyte aggregation-inhibiting and/or lipid-sinking action.

8. Pharmaceutical compositions containing a compound of formula I according to claim 1, as well as per se known pharmacologically acceptable carrier and adjuvant materials.

9. Compounds of formula I according to claim 1 for the combating of metabolic diseases.