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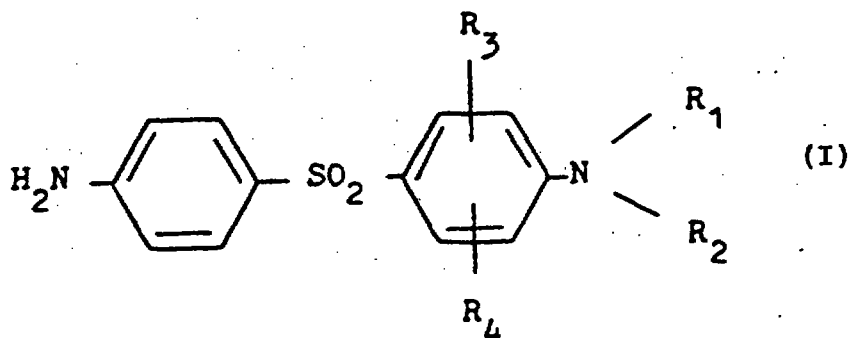
Dr.Fl/Kp

Foreign filing text

New substituted bis-(4-aminophenyl)-
sulfones the preparation thereof and their
use as pharmaceutical compositions

US-A-2.385.899 describes the compound bis-(4-aminophenyl)-sulfone which has an inhibiting effect on the growth of bacteria, mycobacteria and plasmodia.

It has now been found that the new substituted bis-(4-aminophenyl)-sulfones of general formula



and the acid addition salts thereof, particularly the physiologically acceptable acid addition salts thereof, have superior biological properties particularly in terms of their tolerance and their inhibiting effect on bacteria, mycobacteria and plasmodia.

In general formula I above

R_1 represents a hydrogen atom, an alkyl group with 1 to 7 carbon atoms or a cycloalkyl group with 3 to 7 carbon atoms,

R_2 represents a hydrogen atom or an alkyl group with 1 to 3 carbon atoms,

R_3 represents a nitrile, alkylaminocarbonyl, dialkylamino-

carbonyl, N-cycloalkyl-alkylaminocarbonyl, alkylamino, dialkylamino, dialkylaminocarbonylalkoxy, alkylamino-sulfonyl, dialkylaminosulfonyl, hydroxyalkyl, alkyl-carbonyl, aminoalkyl or alkoxyalkyl group

or, if R_1 and R_2 represent hydrogen atoms, a hydroxy or hydroxycarbonylalkoxy group

or, if R_1 represents an alkyl or cycloalkyl group and R_2 represents a hydrogen atom or an alkyl group, it may also represent a halogen atom or a trifluoromethyl, nitro, amino, aminosulfonyl, aminocarbonyl, alkyl, carboxy or alkoxy carbonyl group and

R_4 represents a hydrogen atom or, if R_1 and R_2 both represent hydrogen atoms and R_3 in the 2 position represents a halogen atom or a hydroxy group, R_4 may also represent a halogen atom or a hydroxy or alkoxy group, whilst the alkyl parts mentioned in the definitions of the groups R_3 and R_4 hereinbefore may each contain 1 to 3 carbon atoms and the cycloalkyl part may contain from 3 to 7 carbon atoms.

The present invention thus relates to the new compounds of general formula I above, the acid addition salts thereof, particularly the acid addition salts thereof with physiologically acceptable inorganic or organic acids, pharmaceutical compositions containing these compounds or the physiologically acceptable acid addition salts thereof and the preparation thereof.

This invention further relates to the new combinations of the new substituted bis(4-aminophenyl)-sulfones of general formula I above and the physiologically acceptable acid addition salts thereof

with a dihydrofolic acid-reductase inhibitor such as pyrimethamine, trimethoprim or trimethoprim derivatives.

By way of example of the definitions of the groups R_1 to R_4 given hereinbefore,

R_1 may represent a hydrogen atom, a methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, n-pentyl, isoamyl, n-hexyl, n-heptyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl group,

R_2 may represent a hydrogen atom or a methyl, ethyl, n-propyl or isopropyl group,

R_3 may represent a cyano, methylaminocarbonyl, ethylaminocarbonyl, isopropylaminocarbonyl, dimethylaminocarbonyl, diethylaminocarbonyl, di-n-propylaminocarbonyl, N-methylethylaminocarbonyl, N-methyl-cyclopentylaminocarbonyl, N-methyl-cyclohexylaminocarbonyl, N-methyl-cycloheptylaminocarbonyl, N-ethyl-cyclohexylaminocarbonyl, methylamino, ethylamino, n-propylamino, isopropylamino, dimethylamino, diethylamino, diisopropylamino, N-methyl-ethylamino, N-ethyl-n-propylamino, dimethylaminocarbonylmethoxy, diethylaminocarbonylmethoxy, 2-dimethylaminocarbonylethoxy, 2-diethylaminocarbonylethoxy, methylaminosulfonyl, ethylaminosulfonyl, isopropylaminosulfonyl, dimethylaminosulfonyl, diethylaminosulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxypropyl, 3-hydroxypropyl, methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, aminomethyl, 2-aminoethyl, 3-aminopropyl, methoxymethyl, 2-methoxyethyl, ethoxymethyl, 2-ethoxyethyl, n-propoxymethyl, 2-n-propoxyethyl, hydroxy, hydroxycarbonylmethoxy, 2-hydroxycarbonylethoxy, 3-hydroxycarbonylpropoxy, 2-dimethylaminoethoxy, 2-diethylaminoethoxy, trifluoromethyl, nitro, amino, aminosulfonyl, aminocarbonyl, methyl, ethyl, n-propyl, isopropyl, carboxy, methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl

or isopropoxycarbonyl group or a fluorine, chlorine, bromine or iodine atom and

R_4 represents a hydrogen, fluorine, chlorine, bromine or iodine atom or a hydroxy, methoxy, ethoxy or n-propoxy group.

Preferred compounds of general formula I above are those wherein

R_1 represents a hydrogen atom, an alkyl group containing 1 to 7 carbon atoms or a cycloalkyl group containing 4 to 7 carbon atoms,

R_2 represents a hydrogen atom or a methyl group,

R_3 represents a nitrile, methylaminocarbonyl, N-cyclohexyl-methylaminocarbonyl, methylamino, dimethylamino, dimethylaminocarbonylmethoxy, hydroxymethyl, hydroxyethyl, methylcarbonyl, aminocarbonyl or methoxymethyl group

or, if R_1 and R_2 both represent hydrogen atoms, R_3 may also represent a hydroxy or hydroxycarbonylmethoxy group

or, if R_1 represents an alkyl or cycloalkyl group and R_2 represents a hydrogen atom or a methyl group, R_3 may also represent a chlorine or bromine atom or a methyl, trifluoromethyl, nitro, amino or aminocarbonyl group and

R_4 represents a hydrogen atom or, if R_1 and R_2 both represent hydrogen atoms and R_3 in the 2 position represents a hydroxy group or a chlorine or bromine atom, R_4 may also represent a chlorine or bromine atom or a hydroxy or methoxy group.

However, the particularly preferred compounds of general formula I are those wherein

R_1 represents a hydrogen atom, an alkyl group with 1 to 3 carbon atoms or a cycloalkyl group with 4 to 7 carbon atoms,

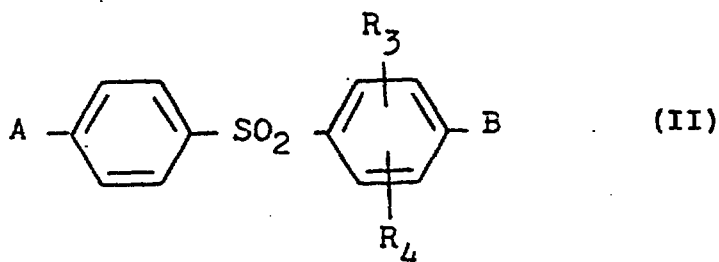
R_2 represents a hydrogen atom or, if R_1 represents a methyl group, R_2 may also represent a methyl group,

R_3 in the 2 position represents a chlorine or bromine atom or a methyl, trifluoromethyl, hydroxymethyl, hydroxyethyl, methylamino, dimethylamino, cyano or methylcarbonyl group and

R_4 represents a hydrogen atom.

According to the invention the new compounds are obtained by the following processes:

a) Reduction of a compound of general formula



wherein

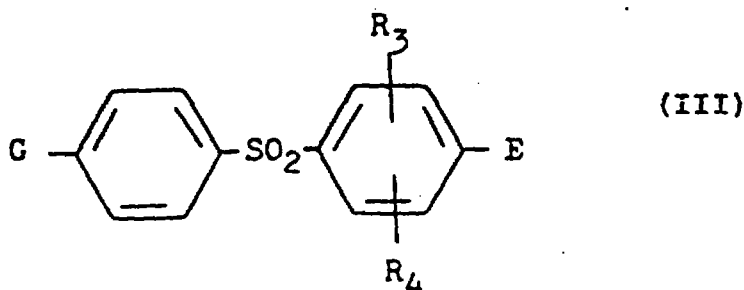
R_3 and R_4 are as hereinbefore defined, one of the groups A or B represents a nitro group and the other group A or B represents a

$\begin{matrix} R_1 \\ R_2 \end{matrix} \diagup \text{N}$ group, wherein R_1 and R_2 are as hereinbefore

defined, or also represents a nitro group.

The reduction is conveniently carried out in a solvent or mixture of solvents such as water, methanol, ethanol, glacial acetic acid, ethyl acetate, dimethylformamide, water/ethanol or water/tetrahydrofuran in the presence of a reducing agent, e.g. with hydrogen in the presence of a hydrogenation catalyst such as Raney nickel, platinum or palladium/charcoal, with metals such as iron, tin or zinc in the presence of an acid such as hydrochloric or acetic acid, with salts such as iron(II)sulphate, tin(II)chloride/hydrochloric acid or sodium dithionite in the presence of a base such as sodium hydroxide solution or pyridine or with hydrazine in the presence of Raney nickel, at temperatures of between 0 and 50°C, preferably at ambient temperature.

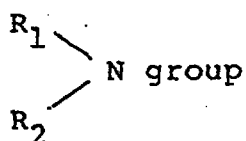
b). Cleaving one or two protecting groups from a compound of general formula



wherein

R_3 and R_4 are as hereinbefore defined,

E represents an amino, alkylamino or cycloalkyl-amino group protected by a protecting group, wherein the alkyl part may contain from 1 to 7 carbon atoms and the cycloalkyl part may contain from 3 to 7 carbon atoms, or a



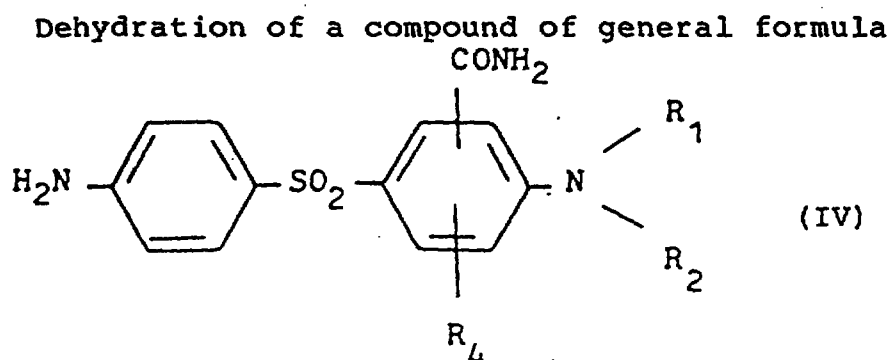
wherein R_1 and R_2 are as hereinbefore defined,
and

G represents an amino group optionally protected by a protecting group, but at least one of the groups E or G must represent one of the above-mentioned groups protected by a protecting group.

Suitable protecting groups are the protecting groups conventionally used for amino groups, e.g. hydrolytically removable protecting groups such as the acetyl, propionyl, benzoyl, p-toluenesulfonyl, methanesulfonyl or ethoxycarbonyl group, or hydrogenolytically removable groups such as the benzyl group.

Any protecting group used is preferably split off by hydrolysis, e.g. with an acid such as hydrochloric, sulphuric or phosphoric acid or with a base such as sodium hydroxide or potassium hydroxide in a suitable solvent or mixture of solvents such as water, water/methanol, ethanol, water/ethanol, water/isopropanol or water/dioxan at temperatures of between -10 and 120°C , preferably at temperatures of between ambient temperature and the boiling temperature of the reaction mixture, or by hydrogenolysis, e.g. with hydrogen in the presence of a hydrogenation catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, glacial acetic acid, ethyl acetate, dioxan or dimethylformamide at temperatures of between 0 and 50°C , preferably at ambient temperature.

c) In order to prepare compounds of general formula I wherein R_3 represents a cyano group:



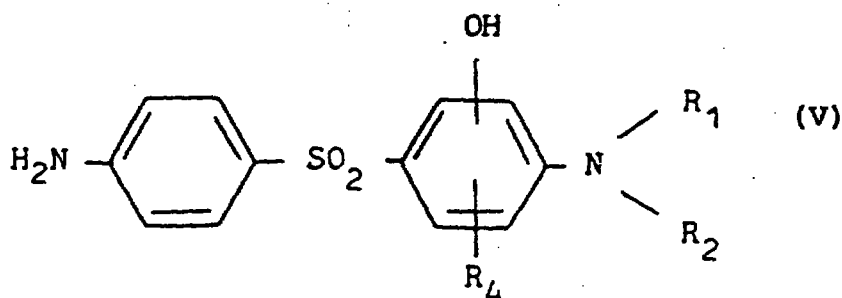
wherein

R_1 , R_2 and R_4 are as hereinbefore defined.

The dehydration is conveniently carried out with a dehydrating agent such as phosphorus pentoxide, concentrated sulphuric acid, p-toluenesulphonic acid, thionylchloride, phosphorus oxychloride, sulfurylchloride, phosphoric acid or dicyclohexylcarbodiimide, optionally in a solvent such as methylene chloride, pyridine or chlorobenzene or in an excess of the dehydrating agent used such as thionyl chloride, phosphorus oxychloride, sulfurylchloride, or phosphoric acid at temperatures of between 0 and 100°C, but preferably at temperatures of between 20 and 80°C. However, the reaction may also be carried out without a solvent.

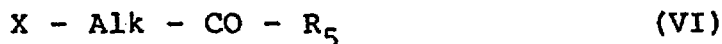
d) In order to prepare compounds of general formula I wherein R_3 represents a hydroxycarbonylalkoxy or dialkylaminocarbonyl-alkoxy group:

Alkylation of a compound of general formula



wherein

R_1 , R_2 and R_4 are as hereinbefore defined, with a compound of general formula



wherein

Alk represents an alkylene group with 1 to 3 carbon atoms,

R_5 represents a hydroxy, alkoxy or dialkylamino group wherein the alkyl part may contain 1 to 3 carbon atoms, and

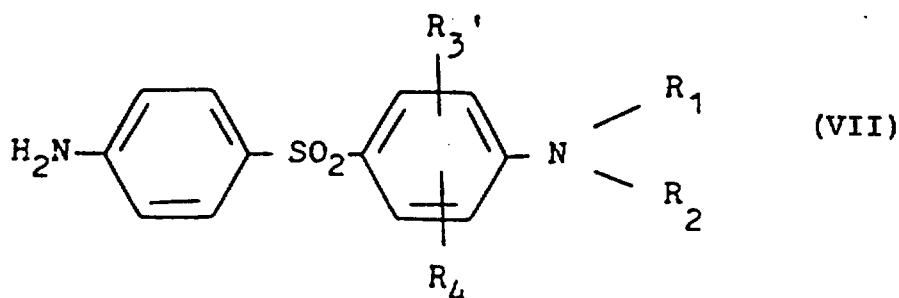
X represents a nucleophilically exchangeable group such as a chlorine or bromine atom, optionally with subsequent hydrolysis.

The reaction is preferably carried out in a solvent such as diethylether, tetrahydrofuran, dioxan, methanol, ethanol, pyridine or dimethylformamide, optionally with a base such as sodium hydride, potassium hydride, potassium carbonate or potassium tert.butoxide at temperatures of between 0 and 75°C, preferably at ambient temperature.

The optional subsequent hydrolysis is preferably carried out either with an acid such as hydrochloric, sulphuric, phosphoric or trichloroacetic acid or with a base such as sodium hydroxide or potassium hydroxide in a suitable solvent such as water, water/methanol, ethanol, water/ethanol, water/isopropanol or water/dioxan at temperatures of between -10°C and 120°C, e.g. at temperatures of between ambient temperature and the boiling temperature of the reaction mixture.

e) In order to prepare compounds of general formula I wherein R_3 represents an aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl or dialkylaminocarbonyl-alkoxy group:

Reaction of a compound of general formula



wherein

R_1 , R_2 and R_4 are as hereinbefore defined and

R_3 represents a hydroxycarbonyl or hydroxycarbonyl-alkoxy group, or a reactive derivative thereof, with an amine of general formula



wherein

R_6 represents a hydrogen atom or an alkyl group containing 1 to 3 carbon atoms and

R_7 represents a hydrogen atom or an alkyl group containing 1 to 3 carbon atoms, or the reactive derivatives thereof.

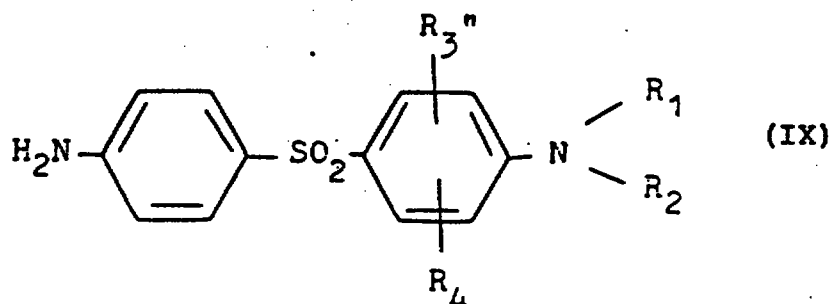
The reaction is conveniently carried out in a solvent such as methylene chloride, chloroform, carbon tetrachloride, ether, tetrahydrofuran, dioxan, benzene, toluene, acetonitrile or dimethylformamide, optionally in the presence of an acid-activating agent or a dehydrating agent, e.g. in the presence of ethylchloroformate, thionylchloride, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxy succinimide, N,N'-carbonyldiimidazole or N,N'-thionyl-diimidazole or triphenylphosphine/carbon tetrachloride, or an agent which activates the amino group, e.g. phosphorus trichloride, and optionally in the presence of an inorganic base such as sodium carbonate or a tertiary organic base such as triethylamine or pyridine, which may simultaneously serve as solvent, at temperatures of between -25°C and 250°C , but preferably at temperatures of between -10°C and the boiling temperature of the solvent used. The reaction may also be carried out without a solvent

and furthermore any water formed during the reaction may be removed by azeotropic distillation, e.g. by heating with toluene using a water separator or by adding a drying agent such as magnesium sulphate or molecular sieve.

In this reaction it may also be advantageous to prepare an activated derivative of a compound of general formula VII or VIII in the reaction mixture initially and then react this derivative with a compound of general formula VIII or VII.

f) In order to prepare compounds of general formula I wherein R_3 represents a hydroxymethyl, aminomethyl or 1-hydroxyalkyl group:

Reduction of a compound of general formula



wherein

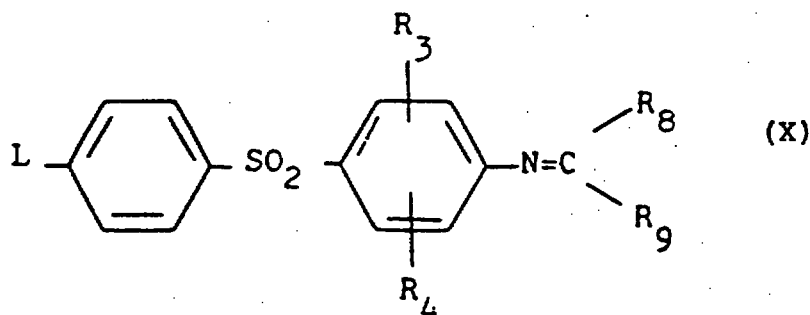
R_1 , R_2 and R_4 are as hereinbefore defined and

R_3'' represents a hydroxycarbonyl, alkoxycarbonyl, aminocarbonyl or alkylcarbonyl group, whilst the alkylcarbonyl group may contain a total of 2 to 4 carbon atoms.

The reaction is preferably carried out with a metal hydride such as sodium borohydride, lithium aluminium hydride or diborane in a solvent such as water, methanol, water/methanol, diethyl ether, tetrahydrofuran or dioxan at temperatures of between 0 and 80°C, preferably at temperatures of between ambient temperature and 70°C.

g) In order to prepare compounds of general formula I wherein R_1 represents an alkyl or cycloalkyl group and R_2 represents a hydrogen atom:

Reduction of a compound of general formula



wherein

R_3 and R_4 are as hereinbefore defined,

L represents an amino or nitro group and

R_8 and R_9 together with the carbon atom between them represent an alkylidene group with 1 to 7 carbon atoms or a cycloalkylidene group with 3 to 7 carbon atoms.

The reduction is preferably carried out in a suitable solvent such as methanol, ethanol, methanol/water, ethyl acetate, tetrahydrofuran or dioxan with nascent or catalytically activated hydrogen or with a hydride such as diborane, sodium borohydride or lithium aluminium hydride at temperatures of between 0 and 50°C, preferably at ambient temperature.

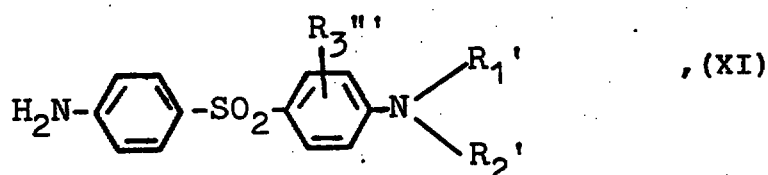
If L represents the nitro group, the reduction is particularly advantageously carried out in a solvent such as methanol or ethyl acetate with hydrogen in the presence of a hydrogenation catalyst such as platinum or palladium/charcoal and under a hydrogen pressure of 0 to 5 bar or with a complex metal hydride such as lithium aluminium hydride or diborane at temperatures of between 0 and 50°C, preferably at ambient temperature.

If L in a compound of general formula X represents the amino group, the reduction is carried out particularly

advantageously in a solvent such as methanol, methanol/water, tetrahydrofuran or dioxan with a complex metal hydride such as sodium borohydride or lithium aluminium hydride at temperatures of between 0 and 50°C, but preferably at ambient temperature.

h) In order to prepare compounds of general formula I wherein at least one of the radicals R_1 or R_2 does not represent a hydrogen atom and R_3 represents a halogen atom or an alkylamino, dialkylamino, hydroxyalkyl, aminoalkyl, alkoxyalkyl, hydroxy, amino, trifluoromethyl or alkyl group:

Reduction of a compound of general formula



wherein

R_1' and R_2' have the meanings given hereinbefore for R_1 and R_2 with the proviso that one of the radicals R_1' or R_2' represents an alkanoyl group with 1 to 7 carbon atoms and

R_3'' represents a halogen atom or an alkylamino, dialkylamino, hydroxyalkyl, aminoalkyl, alkoxyalkyl, hydroxy, amino, trifluoromethyl or alkyl group, wherein each alkyl part may contain 1 to 3 carbon atoms.

The reduction is preferably carried out in a solvent such as methanol, ethanol, ether, tetrahydrofuran or dioxan with a suitable reduction agent such as a metal hydride, e.g. with lithium aluminium hydride, with sodium-bis-(methoxyethoxy)-aluminium hydride, with sodium borohydride in the presence of a lewis

acid such as aluminium chloride, titanium(IV)chloride or cobalt(II)chloride, with sodium borohydride in the presence of trifluoroacetic acid, acetic acid or pyridine, with diborane or borane/dimethylsulfide, at temperatures of between -10°C and 120°C , preferably at temperatures of between 0°C and the boiling temperature of the solvent used.

If according to the invention a compound of general formula I is obtained wherein R_3 represents an alkoxycarbonyl or alkoxycarbonylalkoxy group, this may be converted by hydrolysis into a corresponding compound of general formula I wherein R_3 represents a hydroxycarbonyl or hydroxycarbonylalkoxy group, or

if a compound of general formula I is obtained wherein R_3 and/or R_4 represent a chlorine or bromine atom, this may be converted by hydrolysis or alcoholysis into a corresponding compound of general formula I wherein R_3 in the 2 position represents a hydroxy or alkoxy group and R_4 represents a chlorine or bromine atom.

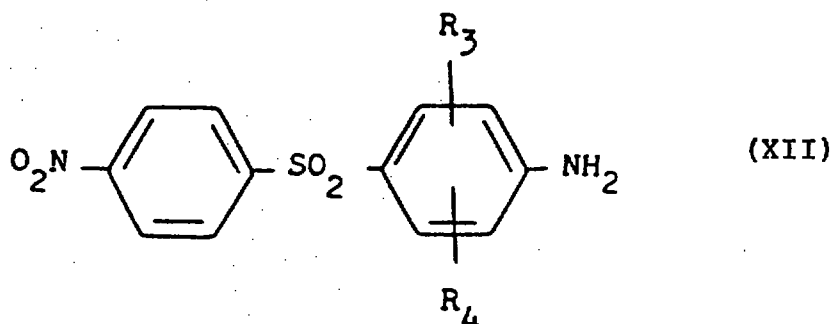
This hydrolysis is conveniently carried out either with an acid such as hydrochloric or sulphuric acid or with a base such as sodium hydroxide or potassium hydroxide in a suitable solvent such as water, water/methanol, ethanol, water/ethanol, water/isopropanol or water/dioxan at temperatures of between -10°C and 120°C , e.g. at temperatures of between ambient temperature and the boiling temperature of the reaction mixture.

The alcoholysis is conveniently carried out in a corresponding alcohol as the solvent such as methanol, ethanol or propanol, optionally in a pressure vessel, preferably with a base such as sodium hydroxide or potassium hydroxide at temperatures of between 20°C and 200°C , preferably at temperatures of between 50 and 180°C .

(15)

The compounds of general formulae II to XI used as starting materials are known from the literature or may be obtained by methods known from the literature.

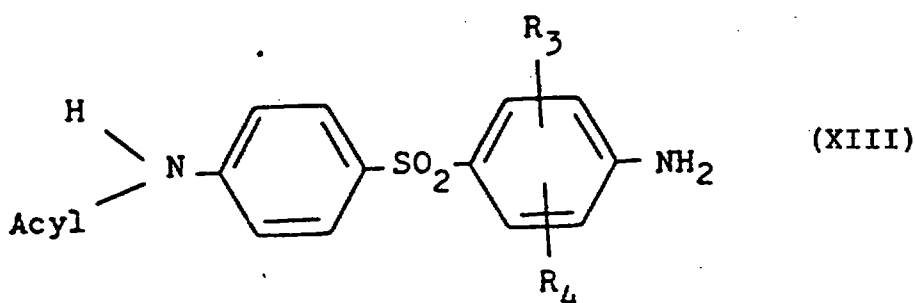
Thus, for example, a compound of general formula II or III may be obtained by reacting an alkali metal salt of a corresponding acylaminophenyl-sulfinic acid with a corresponding halonitrobenzene. A compound of general formula



optionally obtained after splitting off an acyl group used as the protecting group, wherein

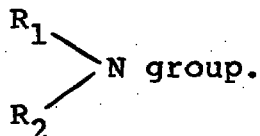
R_3 and R_4 are as hereinbefore defined, may subsequently be converted by reductive amination into a compound of general formula II or after tosylation, subsequent alkylation and reduction of the nitro group and optionally subsequent acylation into a compound of general formula III or XI.

Moreover, a compound of general formula

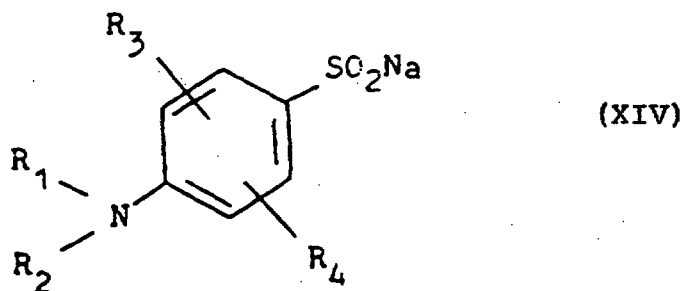


prepared by methods known from the literature, wherein R_3 and R_4 are as hereinbefore defined and Acyl represents an organic acyl group, may be converted by reductive amination or by reduction of a Schiff's

base obtained after reaction with a corresponding carbonyl compound into a compound of general formula III wherein D represents an aminoacyl group and E represents a



Moreover, a compound of general formula



wherein

R_1 to R_4 are as hereinbefore defined and Na represents a sodium ion, may be reacted with a 4-halonitrobenzene to form a corresponding diphenylsulfone of general formula III.

A cycloalkylamino compound of general formula II, however, is preferably obtained by reductive amination of a corresponding amino compound with a cycloalkanone in the presence of sodium cyanoborohydride or by reduction of the corresponding Schiff's base with a complex metal hydride.

A compound of general formula X used as starting material is obtained by reacting a corresponding compound of general formula XII with a corresponding carbonyl derivative, optionally in the presence of titanium(IV) chloride and optional subsequent reduction of the nitro group, for example with catalytically activated hydrogen.

As already mentioned hereinbefore, the new compounds of general formula I and the acid addition salts thereof with physiologically acceptable inorganic

or organic acids have an inhibiting effect on the growth of bacteria and parasites such as plasmodia and mycobacteria thanks to their inhibiting effect on 7,8-dihydropteroic acid-synthetase.

For example the following compounds

A = 4-Ethylamino-4'-amino-2-chloro-diphenylsulfone,
B = 4'-Amino-2-chloro-4-isopropylamino-diphenylsulfone,
C = 4-Ethylamino-4'-amino-2-methyl-diphenylsulfone,
D = 4-Ethylamino-4'-amino-2-trifluoromethyl-diphenylsulfone,
E = 4,4'-Diamino-2-hydroxymethyl-diphenylsulfone
F = 4,4'-Diamino-2-(1-hydroxyethyl)-diphenylsulfone,
G = 4,4'-Diamino-2-(N,N-dimethylamino)-diphenylsulfone,
H = 4,4'-Diamino-2-(N-methylamino)-diphenylsulfone,
I = 4,4'-Diamino-2-cyano-diphenylsulfone,
K = 4,4'-Diamino-2-methylcarbonyl-diphenylsulfone,
L = 4'-Amino-2-methyl-4-methylamino-diphenylsulfone
and
M = 4'-Amino-2-methyl-4-propylamino-diphenylsulfone
were tested for their biological activity in cell-free enzyme extract of Plasmodium berghei as follows:

1. Preparation of the enzyme extract

Plasmodia are isolated from mouse blood infected with Plasmodium berghei in accordance with the following reference (Heidrich, H.-G. et al., Z.Parasitenkd. 59:151(1979)). The plasmodia were opened by ultrasound. Proteins with 7,8-hydropteroic acid synthetase activity are concentrated by gel filtration.

2. Biological test system

The inhibiting effect on 7,8-dihydropteroic acid synthesis of plasmodia is determined as follows:

Under optimum reaction conditions, i.e. $V_{\max}$ for the reaction which is to be inhibited, the concentration of inhibitor in the new compounds

resulting in a 50% reduction in the enzyme synthesis performance is determined. For this purpose the quantity of 7,8-dihydropteroic acid synthesised from the enzyme extract is determined by means of high performance liquid chromatography (HPLC) using a UV detector after an incubation period of 4 hours. It was established that the synthesis of 7,8-dihydropteroic acid proceeded in a linear manner during this period.

The i_{50} values obtained by this method for a selection of the compounds claimed and those of the comparison preparations bis(4-aminophenyl)sulfone (Dapsone[®], DDS) and N¹-(5,6-dimethoxy-4-pyrimidinyl)-sulfanilamide (Fanasil[®]) are given in the following Table:

Substance	i_{50} [μ M]
A	2.10
B	2.67
C	2.62
D	5.86
E	4.90
F	10.40
G	12.90
H	4.10
I	12.48
K	12.90
L	2.94
M	2.44
Dapsone [®]	12.41
Fanasil [®]	200

Moreover, in contrast to Dapsone[®], the new compounds are well tolerated and in particular show a very low methaemoglobin

formation. For example, when substances I and M were administered to cats in a dosage of 200 mg/kg by oral route no methaemoglobin formation could be detected.

On the basis of their biological properties the new compounds and the physiologically acceptable acid addition salts thereof are suitable for the treatment of bacterial diseases, malaria and leprosy.

In monotherapy the single dosage for adults is from 100 to 300 mg, preferably 100 to 200 mg, once or twice a day; in combined therapy with a dihydrofolic acid-reductase inhibitor the single dose for adults is 50 to 200 mg + 5 to 30 mg of pyrimethamine, but preferably 50 to 150 mg + 6.25 to 25 mg of pyrimethamine.

The new compounds and the physiologically acceptable acid addition salts thereof optionally combined with a dihydrofolic acid reductase inhibitor such as pyrimethamine, trimethoprim or a trimethoprim derivative, may be made into the usual galenic preparations such as plain or coated tablets, capsules or suspensions.

The following Examples serve to illustrate the invention:

the mixture is stirred into 50 ml of 10 N sodium hydroxide solution whilst being intensively cooled. The product precipitated is suction filtered and dried. The crude product is purified by column chromatography. For this, the substance is dissolved in ethyl acetate and chromatographed over 200 g of silica gel (0.063-0.2 mm), ethyl acetate and methylene chloride 1:1 being used as eluant. The corresponding fractions are combined and evaporated. Colourless crystals, m.p.: 240-242°C.

Example 2

4,4'-Diamino-2,6-dibromo-diphenylsulfone

a) 3,4,5-Tribromonitrobenzene

At 20°C, with stirring and cooling with ice, a solution of 47.2 g of 2,6-dibromo-4-nitro-aniline in 1.6 litres of acetic acid is slowly poured into a solution of 12 g of sodium nitrite in 85 ml of concentrated sulphuric acid. Then the mixture is stirred for 20 minutes at ambient temperature. The solution thus prepared is then slowly added with stirring and cooling with ice to a solution of 12.8 g of copper(I) bromide in 40 ml of 63% hydrobromic acid. After it has all been added the mixture is stirred for a further 30 minutes. It is diluted with water, the precipitate is filtered off and washed with water. This crude product is recrystallised from methanol. Colourless crystals, m.p. 110°C.

b) 4'-Acetamino-2,6-dibromo-4-nitro-diphenylsulfide

2.9 g of sodium are dissolved in 520 ml of absolute ethanol. 22 g of 4-acetamino-thiophenol are dissolved in the sodium alkoxide solution thus prepared, then 44.5 g of 3,4,5-tribromonitrobenzene are added the mixture is then heated to reflux

Example 1

3-Cyano-4,4'-diamino-diphenylsulfone

a) 3-Cyano-4,4'-dinitro-diphenylsulfide

a) 10 g (0.064 mol) of 4-nitrothiophenol are dissolved by stirring in a solution of 2.8 g of sodium hydroxide in 10 ml of water and 100 ml of ethanol. Then 11.8 g (0.064 mol) of 5-chloro-2-nitrobenzonitrile are added in order to reflux the resulting solution for 1 hour with stirring, whereupon a yellow substance is precipitated. After the suspension has been cooled the product obtained is suction filtered, washed with ethanol and then dried. This crude product is recrystallised from methanol.

Yellow crystals, m.p.: 123-126°C.

b) 3-Cyano-4,4'-dinitro-diphenylsulfone

10 g (0.033 mol) of 3-cyano-4,4'-dinitro-diphenylsulfide are dissolved by heating in 150 ml of glacial acetic acid. 20 ml of perhydrol are added dropwise to this solution with stirring at ambient temperature. After it has all been added the mixture is refluxed for a further 1½ hours during which a white substance is precipitated. After the suspension has cooled the substance is suction filtered, washed with ethanol and water and then dried.

Yellow crystals, m.p.: 188-190°C.

c) 3-Cyano-4,4'-diamino-diphenylsulfone

2 g (0.006 mol) of 3-cyano-4,4'-dinitro-diphenylsulfone are added in batches, with stirring, at 10 to 20°C, to a mixture of 8.1 g of $\text{SnCl}_2 \times 2\text{H}_2\text{O}$ and 15 ml of conc. hydrochloric acid. After it has all been added the mixture is stirred for a further 4 hours at ambient temperature and then

temperature for 5 hours. After cooling it is poured onto water, extracted exhaustively with ethyl acetate, the combined ethyl acetate extracts are washed with water, dried over sodium sulfate and evaporated down to a small volume. The material precipitated is suction filtered and recrystallised from methanol. Colourless crystals, m.p.: 208-209°C.

c) 2,6-Dibromo-4,4'-dinitro-diphenylsulfone

5 g of 4'-acetamido-2,6-dibromo-4-nitro-diphenylsulfide are dissolved in 40 ml of glacial acetic acid by heating. 20 ml of perhydrol are added dropwise to this solution at ambient temperature with stirring. After it has all been added the mixture is stirred at reflux temperature for a further 2 hours. On cooling, yellow crystals are precipitated which are suction filtered and washed first with water and then with methanol. M.p.: 170-175°C.

d) 4,4'-Diamino-2,6-dibromo-diphenylsulfone

17 g of tin(II) chloride dihydrate are dissolved in 17 ml of concentrated hydrochloric acid. 3.96 g of 2,6-dibromo-4,4'-dinitro-diphenylsulfone are added to this solution with a spatula, with stirring, and the temperature rises to about 50°C. The mixture is stirred for a further 2 hours and left to stand for 16 hours at ambient temperature. Then it is slowly poured into 40 ml of a 10 N sodium hydroxide solution with stirring and cooling with ice. The precipitate is filtered off and washed thoroughly with water and then with isopropanol. Colourless crystals, m.p.: 168-170°C (decomp.).

Example 3

4,4'-Diamino-2-hydroxy-6-methoxy-diphenylsulfone

1 g of 4,4'-diamino-2,6-dibromo-diphenylsulfone

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(Example 2) are added to 1.12 g of potassium hydroxide in 0.15 ml of water and 25 ml of methanol. This mixture is heated to 150°C under pressure for 14 hours. It is then diluted with water, the insoluble matter is filtered off and the filtrate is concentrated to dryness in vacuo. The solid residue is taken up in a little water. The aqueous solution is acidified with 2N hydrochloric acid up to pH 5 and the colourless precipitate obtained is suction filtered, washed with water and dried.
M.p.: 127°C (decomp.).

Example 4

2-Bromo-4,4'-diamino-6-hydroxy-diphenylsulfone

1 g of 4,4'-diamino-2,6-dibromo-diphenylsulfone (Example 2) are added to a solution of 1.12 g of potassium hydroxide in 0.15 ml of water and 50 ml of tert.butanol. This mixture is heated to 150°C under pressure for 10 hours. It is then diluted with water, filtered to remove the insoluble matter and the filtrate is evaporated to dryness in vacuo. The solid residue is taken up in a little water. The aqueous solution is acidified with 2N hydrochloric acid up to pH 5 and the colourless precipitate obtained is suction filtered and washed with water and dried.

IR spectrum (KBr): 3000 - 3600 cm⁻¹ OH assoc.
 3360, 3470 cm⁻¹ NH₂ free
 3210 cm⁻¹ NH₂ assoc.
 2840 cm⁻¹ OCH₃
 1140, 1320 cm⁻¹ SO₂

Example 5

4-Ethylamino-4'-amino-2-methyl-diphenylsulfone

a) 4'-Acetamino-2-methyl-4-tosylamino-diphenylsulfide

2.7 g of 4'-acetamino-4-amino-2-methyl-diphenyl-

sulfide (J. org. Chem. 15, 400 (1950)) are dissolved in 7 ml of dry pyridine. At ambient temperature, 2.85 g of p-toluenesulfonic acid chloride are added to this solution and the mixture is left to stand for 2 days at ambient temperature. Then it is heated to 90°C for 6 hours to complete the reaction and after cooling it is diluted with about 50 ml of water. The solids precipitated are suction filtered and carefully washed with water and then with petroleum ether and dried.

M.p.: 130-134°C

b) 4'-Acetamino-4-(N-ethyl-N-tosyl-amino)-2-methyl-diphenylsulfide

3.5 g of 4'-acetamino-2-methyl-4-tosylamino-diphenylsulfide, 2 g of ethyl iodide and 1.5 g of dry potassium carbonate are heated to 95°C in 50 ml of dimethylformamide with stirring for 17 hours. After cooling the mixture is poured onto water. The solids precipitated are suction filtered and washed thoroughly with water and petroleum ether and then dried.

IR spectrum (methylene chloride): 3420 cm^{-1} NH
1695 cm^{-1} amide
1505 cm^{-1} sulfonamide

b) 4'-Acetamino-4-(N-ethyl-tosylamino)-2-methyl-diphenylsulfone

2.25 g of 4'-acetamino-4-(N-ethyl-tosylamino)-2-methyl-diphenylsulfide are heated to 90°C for 3 hours in 20 ml of acetic acid and 6 ml of perhydrol. After cooling, the mixture is diluted with water, the solids precipitated are carefully washed with water and petroleum ether and dried. This crude product is chromatographed over silica gel with a methylene chloride/methanol mixture (25:1). Light yellow foamy substance.

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IR spectrum (KBr):	3420 cm ⁻¹	NH
	1680 cm ⁻¹	amide
	1500 cm ⁻¹	sulfonamide
	1315, 1150 cm ⁻¹	sulfone

e) 4-Ethylamino-4'-amino-2-methyl-diphenylsulfone

1.05 g of 4'-acetamino-4-(N-ethyl-tosylamino)-2-methyl-diphenylsulfone are dissolved in 6 ml of concentrated sulfuric acid. This solution is left to stand for 4 hours at ambient temperature, then mixed with ice and neutralised with ammonia. The solids precipitated are suction filtered. The crude product consisting of 4'-acetamino-4-ethylamino-2-methyl-diphenylsulfone is heated to boiling temperature for 1 hour in a mixture of concentrated hydrochloric acid/water = 1/1. After cooling, it is poured onto water and neutralised with ammonia. The solids precipitated are washed with water and dried.

M.p.: 166-167°C.

Example 6

4'-Amino-2-methyl-4-methylamino-diphenylsulfone

3.5 g of 4'-acetamino-2-methyl-4-(N-methyl-tosyl-amino)-diphenylsulfone, prepared analogously to Example 5, are heated to reflux temperature with 3.5 g of phenol in 120 ml of 48% hydrobromic acid for 1½ hours. After cooling, the mixture is poured onto ice, neutralised with sodium hydroxide, extracted with methylene chloride, dried over sodium sulfate and concentrated to dryness in vacuo. The solid residue is dissolved in absolute ethanol. This solution is acidified with ethanolic hydrochloric acid and then mixed with ether until crystallisation starts. The crystals are suction filtered, washed with ethanol/ether and dried.

Dihydrochloride: colourless crystals, m.p.: 232-235°C.

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M.p. of the base: 150-153°C.

Example 7

4'-Amino-2-methyl-4-n-propylamino-diphenylsulfone

Prepared from 4'-acetamino-2-methyl-4-(N-n-propyl-tosylamino)-diphenylsulfone with phenol and hydrobromic acid analogously to Example 6. Colourless crystals, m.p.: 170-173°C.

Example 8

4-Ethylamino-4'-amino-2-chloro-diphenylsulfone

a) 4'-Acetamino-2-chloro-4-p-tosylamino-diphenylsulfone

190 mg of p-tosyl chloride are dissolved in 5 ml of anhydrous pyridine and 300 mg of 4'-acetamino-4-amino-2-chloro-diphenylsulfone (synthesised according to J. Med. Chem. 14:1166 (1971)) are added. The mixture is kept at ambient temperature for 3 hours with stirring and for 1 hour at 50°C. After cooling, it is poured onto ice/HCl and the precipitate is suction filtered. Recrystallisation from MeOH/H₂O, colourless crystals.

b) 4-Ethylamino-4'-amino-2-chloro-diphenylsulfone

70 mg of 4'-acetamino-2-chloro-4-p-tosylamino-diphenylsulfone and 25 mg of potassium carbonate are suspended in 5 ml DMF. After the addition of 200 ul of ethyl iodide the mixture is heated to 90°C (bath) for 24 hours. After cooling, the mixture is poured onto ice and the precipitate is removed by suction filtering. The dry residue is dissolved in 0.5 ml of conc. H₂SO₄ with stirring. After 1 hour it is poured onto ice and the pH is adjusted to 4 to 6 with ammonia. The precipitate is suction filtered, mixed with 10 ml of 20% hydrochloric acid and refluxed for 1 hour. After cooling, the mixture is neutralised with ammonia and the precipitate

is suction filtered.

Recrystallisation from MeOH/H₂O.

M.p.: 173-175°C.

Example 9

4'-Amino-2-chloro-4-isopropylamino-diphenylsulfone

300 mg of 4'-amino-2-chloro-4-p-tosylamino-diphenylsulfone, 100 mg of potassium carbonate, 500 ul of isopropylbromide and 10 ml DMF are heated to 90°C (bath) for 72 hours. After cooling, the mixture is poured onto ice and the precipitate is suction filtered. The dry residue is dissolved in 0.5 ml of conc. H₂SO₄ with stirring. After 1 hour it is poured onto ice and the pH is adjusted to 4 to 6 with NH₃. The precipitate obtained is suction filtered, mixed with 10 ml of 20% hydrochloric acid and refluxed for 1 hour. After cooling, it is neutralised with ammonia and the precipitate is suction filtered.

Recrystallisation from methanol. Colourless solids.

NMR (DMSO)	1.08 - 1.15	6H	Doublet CH(CH ₃) ₂
90 MHZ	3.4 - 3.7	1H	Multiplet CH(CH ₃) ₂
	6.04	2H	Singlet NH ₂
	6.5 - 6.7	5H	Multiplet NH, aromatic H
	7.4 - 7.5	2H	Doublet, aromatic H
	7.75 - 7.85	1H	Doublet, aromatic H

Example 10

2-Carboxymethyloxy-4,4'-diamino-diphenylsulfone

a) 2-Ethoxycarbonylmethyloxy-4,4'-diamino-diphenylsulfone

7.9 g (0.03 mol) of 4,4'-Diamino-2-hydroxydiphenylsulfone (J. Scientific and Industrial Research 17B, 192 (1958)) are dissolved in 160 ml of tetrahydrofuran; this solution is mixed with 1.3 g (0.03 mol) of sodium hydride under a nitrogen atmosphere and

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with stirring at ambient temperature; the mixture begins to foam and towards the end of the addition a thick crystal slurry is precipitated. By adding 250 ml of dimethylformamide a clear solution is obtained. 3.3 ml (0.03 mol) of ethyl bromoacetate are added dropwise, the mixture is stirred for 3.5 hours at ambient temperature and then evaporated to dryness in vacuo. The residue is stirred with a mixture of water and methylene chloride, whereupon a solid crystalline material is obtained which is suction filtered from the solvent mixture, stirred with methylene chloride/water once more, suction filtered again and dried. The product thus obtained has a melting point of 178 to 183°C.

b) 2-Carboxymethyloxy-4,4'-diamino-diphenylsulfone

2.8 g (0.008 mol) of 2-ethoxycarbonylmethyloxy-4,4'-diamino-diphenylsulfone are heated to boiling for half an hour in a mixture of 280 ml of ethanol, 2.8 g (0.007 mol) of sodium hydroxide and 56 ml of water. The mixture is left to cool, acidified with conc. hydrochloric acid up to a pH of 1, evaporated to dryness in vacuo, then the residue is briefly boiled with alcohol, filtered to remove any insoluble matter, the filtrate is evaporated to dryness in vacuo and the residue is purified by chromatography on silica gel, eluant methylene chloride/methanol (1:1). The product thus obtained is recrystallised from ethanol and then has a melting point of 255-260°C (decomp.).

Example 11

4,4'-Diamino-2-dimethylamino-carbonyl-methyloxy-diphenylsulfone

3.4 g (0.0097 mol) of 2-ethoxycarbonylmethyloxy-4,4'-diamino-diphenylsulfone are dissolved in a mixture of 68 ml of aqueous 40% dimethylamine

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solution and 100 ml of tetrahydrofuran. This solution is left to stand for 3 hours at ambient temperature, then evaporated to dryness in vacuo, the residue obtained is triturated with 100 ml of water, the solid material is suction filtered and recrystallised from ethanol. The product thus obtained has a melting point of 238-244°C (decomp.).

Example 12

4,4'-Diamino-2-methoxymethyl-diphenylsulfone

a) 2-Hydroxymethyl-4-nitro-chlorobenzene

43.2 g (0.215 mol) of 2-carboxy-4-nitro-chlorobenzene are dissolved in 500 ml of absolute tetrahydrofuran, then 30 ml of triethylamine (0.215 mol) are added thereto. This mixture is cooled to -10°C and at this temperature 22 ml of carbethoxy chloride (0.229 mol) are added dropwise thereto. The resulting mixture is stirred for a further hour at -10 to -5°C. The triethylamine hydrochloride formed is filtered off. The tetrahydrofuran solution is added dropwise over a period of 10 minutes at 0°C to a solution of 30 g of sodium borohydride (0.789 mol) in 100 ml of water. The reaction mixture is allowed to come back to ambient temperature with stirring within an hour. The reddish-orange solution obtained is mixed with 2N hydrochloric acid whilst cooling with ice and then extracted with ether. The ether extract is washed with water. After the ether has been evaporated off an oil remains which crystallises after some time.

IR spectrum (methylene chloride): 3610 cm^{-1} OH
1375 cm^{-1} NO₂

b) 2-Methoxymethyl-4-nitro-chlorobenzene

18.7 g (0.1 mol) of 2-hydroxymethyl-4-nitro-chlorobenzene are dissolved in 500 ml of absolute

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tetrahydrofuran and cooled to 0°C. The sodium alkoxide of the above compound is prepared with 4.8 g (0.1 mol) of sodium hydride (55% in oil). After 1 hour's reaction, 14.2 g (0.1 mol) of methyl iodide are added dropwise with stirring at 0°C. The reaction mixture is kept at 0°C for a further 3 hours with stirring. Then it is stirred without a cooling bath until ambient temperature is reached. The solvent is then evaporated off and the residue is taken up in ethyl acetate, the ethyl acetate phase is washed with water, dried and concentrated to dryness in vacuo. The remaining oil is crystallised from ethyl acetate.

NMR (CDCl₃/CD₃OD): 3.6 ppm 3H Singlet
 4.6 ppm 2H Singlet
 80 MHz 7.5-8.75 ppm 3H Multiplet

c) 4'-Acetylamino-4-nitro-2-methoxymethyl-diphenyl-sulfone

6.5 g (0.0327 mol) of 4-acetylanilido sulfinic acid are suspended in 50 ml of ethanol and 1.5 g (0.033 mol) of sodium hydride (55% in oil) are added in batches with stirring. Then the resulting sodium salt of the above acid is precipitated with ether and dried. 6.6 g (0.03 mol) of 4-acetylanilido sodium sulfinate are refluxed with 6.1 g (0.03 mol) of 2-methoxymethyl-4-nitro-chlorobenzene in 25 ml of dimethylformamide for 5 hours. The reaction mixture is then poured onto ice water and extracted with ethyl acetate. The ethyl acetate extract is washed twice with water, dried over sodium sulfate and the ethyl acetate is evaporated off in vacuo. The solid residue is washed with i-propanol and petroleum ether.

IR spectrum (CH₂Cl₂): 3420 cm⁻¹ NH
 1710 cm⁻¹ CO
 1350 + 1530 cm⁻¹ NO₂

1150 + 1320 cm^{-1} SO_2

d) 4'-Acetylamino-4-amino-2-methoxymethyl-diphenyl-sulfone

3.8 g (0.0104 mol) of 4'-acetylamino-4-nitro-2-methoxymethyl-diphenylsulfone are added in batches with 15 minutes to a boiling mixture of 3.4 g (0.061 mol) of iron powder in 25 ml of alcohol, 6 ml of water and 0.05 ml of 36% hydrochloric acid. The mixture is then refluxed for 2 hours. The reaction mixture is cooled, diluted with methanol, filtered over Celite and the methanol is evaporated. The residue is taken up in water and extracted with ethyl acetate. Then the ethyl acetate is evaporated off and an amorphous solid product is left.

IR spectrum: (KBr): 1680 cm^{-1} Amide I
1525 cm^{-1} Amide II
1140, 1320 cm^{-1} SO_2

e) 4,4'-Diamino-2-methoxymethyl-diphenylsulfone

3.5 g (0.01 mol) of 4'-acetylamino-4-amino-2-methoxymethyl-diphenylsulfone are heated to boiling temperature in 3N hydrochloric acid for 15 minutes. The reaction solution is cooled, diluted with water and filtered. The aqueous filtrate is adjusted to pH 8-9 with dilute aqueous ammonia. The precipitate obtained is filtered off and washed with water.

IR spectrum (KBr): 1130 cm^{-1} SO_2
1280 cm^{-1} SO_2

Example 13

4,4'-Diamino-2-methylcarbonyl-diphenylsulfone

Prepared from 4'-acetamino-4-amino-2-methylcarbonyl-diphenylsulfone (prepared analogously to Example 12c and 12d) with hydrochloric acid analogously to Example 12e.

IR spectrum (CH_2Cl_2): 3485, 3390 cm^{-1} NH_2



1695 cm^{-1} Ketone
1290, 1140 cm^{-1} SO_2

Example 14

4,4'-Diamino-2-(1-hydroxyethyl)-diphenylsulfone

1.6 g (0.005 mol) of 4,4'-diamino-2-methylcarbonyl-diphenylsulfone (Example 13) suspended in 75 ml of 90% aqueous methanol are reduced with 0.3 g (0.0075 mol) of sodium borohydride at 20°C. After 30 minutes a clear solution is obtained. The methanol is evaporated off and the aqueous solution is diluted with more water. An oil is precipitated which is extracted with methylene chloride. After the solvent has been evaporated off a white amorphous product remains.

NMR spectrum (CDCl_3): 1.3 ppm 2H Doublet
5.5 ppm 1H Multiplet
80 MHz 6.6-7.9 ppm 7H Multiplet

Example 15

4,4'-Diamino-2-cyano-diphenylsulfone

6.3 g (0.021 mol) of 4,4'-diamino-2-carbamoyl-diphenylsulfone (prepared analogously to Example 18) are refluxed for 8 hours in 45 ml of thionyl chloride. A yellowish-orange solution is obtained and the thionyl chloride is distilled off. A yellow foam remains which is suspended in water and made alkaline with ammonia solution. The base of the title compound thus obtained is suction filtered as an amorphous solid product and washed with water. The crude product is purified by chromatography on a silica gel column. (Eluant: 8 parts methylene chloride, 1 part methanol and 1 part acetone). The corresponding fractions are freed from the eluant and yield an amorphous, yellowish-white solid product.

Mass spectrum (CH_5): $\text{M}^+ 273 \text{ m/z}$

Example 16

4,4'-Diamino-2-aminomethyl-diphenylsulfone

0.35 g (0.0012 mol) of 4,4'-diamino-2-carbamoyl-diphenylsulfone are dissolved in 25 ml of absolute tetrahydrofuran and mixed with 0.15 g (0.0036 mol) of lithium aluminium hydride. The mixture is stirred for 1 hour at 20°C and then heated to 50°C for 8 hours. The lithium aluminium hydride is decomposed with ice water and the reaction mixture is extracted with ether. After the solvent has been evaporated off, a solid yellow product is left behind, which is purified by chromatography over a silica gel column (eluant: 6 parts methylene chloride and 1 part methanol). After the eluant has been evaporated off from the corresponding fractions a yellowish amorphous product is left.

Mass spectrum (CH 5): M^+ 277 m/z

Example 17

4,4'-Diamino-2-hydroxymethyl-diphenylsulfone

0.23 g (0.00075 mol) of 4,4'-diamino-2-methoxy-carbonyl-diphenylsulfone (J. Med. chem. 14, 1168 (1971)) are dissolved in 15 ml of absolute tetrahydrofuran and mixed with 0.07 g (0.0019 mol) of lithium aluminium hydride. The mixture is stirred for 1 hour at 20°C and then heated for 3 hours to 50°C. The excess lithium aluminium hydride is decomposed with water and then the reaction mixture is extracted with ether. After the solvent has been evaporated off, a yellowish-brown oil is left which is purified by chromatography over a silica gel column. (Eluant: 9 parts methylene chloride and 1 part methanol). The corresponding fractions yield a yellowish oil after evaporation of the eluant.

Mass spectrum (CH 5): M^+ 278 m/z

Example 18

4,4'-Diamino-2-(N-methylcarbamoyl)-diphenylsulfone

0.95 g (0.0025 mol) of 4,4'-diamino-2-chloro-carbonyl-diphenylsulfone-dihydrochloride are suspended in 15 ml of methylene chloride and added to a solution of 0.31 g (0.01 mol) of methylamine in 20 ml of methylene chloride. The mixture is stirred overnight at 20°C. Then the methylene chloride is evaporated off and the remaining solid residue is washed out with water. A white amorphous residue is left.

IR spectrum (KBr): 3480 + 3360 cm^{-1} NH_2
 1630 cm^{-1} Amide
 1125 cm^{-1} SO_2

Example 19

2-(N-Cyclohexyl-N-methyl-carbamoyl)-4,4'-diamino-diphenylsulfone

Prepared from 4,4'-diamino-2-chlorocarbonyl-diphenylsulfone-dihydrochloride and N-cyclohexyl-N-methylamine analogously to Example 18.

IR spectrum (CH_2Cl_2): 3490, 3400 cm^{-1} NH_2
 1620-1630 cm^{-1} Amide
 1300, 1140 cm^{-1} SO_2

Example 20

4,4'-Diamino-2-(N,N-dimethylamino)-diphenylsulfone

a) 2-Chloro-5-nitro-N,N-dimethyl-aniline

63 g of paraformaldehyde are placed in 1 litre of 35% formic acid and at 100°C, 60 g of 2-chloro-5-nitro-aniline in 560 ml of 95% formic acid are added in batches thereto. Then the mixture is heated for 2 hours over a steam bath, the reaction mixture is evaporated, mixed with 560 ml of 2N NaOH and 140 g of Na_2SO_3 , extracted with methylene chloride, the organic phase is dried with magnesium sulfate, evaporated to dryness again and purified

by chromatography over a column filled with silica gel. (Eluant: dichloromethane/cyclohexane = 2:1). Yellow oil which is reacted further directly.

b) 4'-Acetamino-2-(N,N-dimethylamino)-4-nitro-diphenylsulfone

24 g of the sodium salt of 4-acetylamino-phenylsulfinic acid, 22 g of 2-chloro-5-nitro-(N,N-dimethyl)-aniline and 120 ml of absolute dimethylformamide are mixed together, refluxed for 28 hours, poured onto water, extracted with ethyl acetate and the organic phase is dried with magnesium sulfate and evaporated in vacuo. The residue is purified over a column filled with silica gel (eluant: dichloromethane/methanol = 50:1). The fractions containing the desired product are evaporated and the residue is triturated with ether.

Yellow crystals. M.p.: 213-216°C.

c) 4'-Amino-2-(N,N-dimethylamino)-4-nitro-diphenylsulfone

10 g of 4'-acetamino-2-(N,N-dimethylamino)-4-nitro-diphenylsulfone are placed in 50 ml of semi conc. hydrochloric acid and heated for about 1 hour over a steam bath until a clear solution is obtained. Then it is cooled, made basic with 2N sodium hydroxide solution, extracted with dichloromethane, the organic phase is dried with magnesium sulfate and concentrated by evaporation. The residue is purified over a column filled with silica gel (eluant: dichloromethane/methanol = 50:1).

Yellow crystals. M.p.: 164-166°C.

d) 4,4'-Diamino-2-(N,N-dimethylamino)-diphenylsulfone

6 g of 4'-amino-2-(N,N-dimethylamino)-4-nitro-diphenylsulfone are hydrogenated in 200 ml of methanol with 0.6 g of Raney nickel for 6 hours at ambient temperature under a pressure of 3 bar.

Then the catalyst is removed by suction filtering, the filtrate is concentrated to dryness in vacuo and purified over a column filled with silica gel (eluant: dichloromethane/methanol = 60:1). Beige crystals; m.p. 196-197°C.

Example 21

4,4'-Diamino-2-(N-methyl-amino)-diphenylsulfone

Prepared from 2-chloro-5-nitro-(N-methyl)-aniline and the sodium salt of 4-acetylamino-phenyl-sulfinic acid analogously to Example 20. Hardened foam.

IR spectrum (methylene chloride): 3500, 3400 cm^{-1} NH_2
1130, 1300 cm^{-1} SO_2

2-Chloro-5-nitro-N-methyl-aniline was obtained as follows:

50 g of 2-chloro-5-nitro-aniline, 82 g of methyl iodide and 123.3 g of sodium carbonate are refluxed for 16 hours in 1.2 litres of ethanol. Then the insoluble precipitate is filtered off, the mother liquor is concentrated by evaporation and the residue is taken up in dichloromethane. The organic phase is washed with water, dried with magnesium sulfate and concentrated in vacuo. The residue is purified over a column filled with silica gel (eluant: dichloromethane/cyclohexane = 1:2). Orange crystals; m.p.: 106-108°C.

Example 22

4'-Amino-2,4-bis-(N,N-dimethyl-amino)-diphenylsulfone

a) 4'-Acetamino-4-amino-2-(N,N-dimethyl-amino)-diphenylsulfone

4.5 g of 4'-acetamino-2-(N,N-dimethyl-amino)-4-nitro-diphenylsulfone are hydrogenated in 200 ml of methanol with 0.45 g of Raney-nickel for two hours at ambient temperature under a pressure of

3 bar. Then the catalyst is filtered off, the filtrate is concentrated by evaporation and the residue is purified over a column filled with silica gel (eluant: dichloromethane/methanol = 30:1). Light brown crystals; M.p.: 117-119°C.

b) 4'-Acetamino-2,4-bis-(N,N-dimethyl-amino)-diphenylsulfone

1.2 g of paraformaldehyde are dissolved in 30 ml of 95% formic acid with heating and 2.3 g of 4'-acetamino-4-amino-2-(N,N-dimethyl-amino)-diphenylsulfone are added. The reaction mixture is kept at 90°C for 12 hours and then concentrated by evaporation in vacuo. 11 ml of 2N sodium hydroxide solution and 2.7 g of Na₂SO₃ are added, the mixture is extracted with ethylacetate, the extract is treated with active charcoal and magnesium sulphate, concentrated to dryness in vacuo and the residue is purified over a column filled with silica gel (eluant: dichloromethane/methanol = 30:1). Colourless oil which is immediately reacted further.

c) 4'-Amino-2,4-bis-(N,N-dimethyl-amino)-diphenylsulfone

1 g of 4'-acetamino-2,4-bis-(N,N-dimethyl-amino)-diphenylsulfone are dissolved in 50 ml of 2N hydrochloric acid and heated for about 45 minutes over a steam bath. Then the mixture is cooled, made basic with 2N NaOH and extracted with methylene chloride. The organic phase is treated with active charcoal and magnesium sulphate, concentrated to dryness in vacuo and the residue is purified over a column filled with silica gel (eluant: dichloromethane/methanol = 50:1). The residue of the desired fraction is triturated with ether. Yellowish crystals; m.p.: 166-168°C.

Example 23

4'-Amino-4-(N-ethyl-amino)-2-trifluoromethyl-diphenylsulfone

a) 4'-Acetamino-4-nitro-2-trifluoromethyl-diphenylsulfone

50 g of the sodium salt of 4-acetamino-phenylsulfinic acid and 48 g of 2-chloro-5-nitro-benzotrifluoride in 260 ml of absolute dimethylformamide are refluxed for about 25 hours. The mixture is then cooled and poured onto about 2 litres of water, extracted with dichloromethane, the organic phase is washed thoroughly with water, dried with magnesium sulphate and concentrated to dryness in vacuo. The residue is triturated with ether.

Light yellow crystals; M.p.: 228-230°C.

b) 4'-Acetamino-4-amino-2-trifluoromethyl-diphenylsulfone

30 g of 4'-acetamino-4-nitro-2-trifluoromethyl-diphenylsulfone are hydrogenated in 800 ml of methanol with 3 g of Raney-nickel for 8 hours 40 minutes at ambient temperature under a pressure of 3 bar. Then the mixture is heated in order to bring the desired product into solution again. The catalyst is removed by suction filtering whilst still warm and the filtrate is concentrated in vacuo.

Beige crystals; M.p.: 220-224°C.

c) 4'-Acetamino-4-(N-ethyl-amino)-2-trifluoromethyl-diphenylsulfone

3 g of 4'-acetamino-4-amino-2-trifluoromethyl-diphenylsulfone, 6.7 g of acetaldehyde, 0.6 g of molten sodium acetate and 3 g of Raney-nickel in 100 ml of ethanol are hydrogenated at 70°C under a pressure of 5 bar for 11 hours. Then the catalyst is filtered off and the filtrate is concentrated to dryness in vacuo. The evaporation residue is purified by chromatography over a column filled with silica gel (eluant: dichloromethane/methanol = 50:1). Colourless crystals; M.p.: 157-159°C.

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d) 4'-Amino-4-(N-ethyl-amino)-2-trifluoromethyl-diphenylsulfone

1.5 g of 4'-acetamido-4-(N-ethyl-amino)-2-trifluoromethyl-diphenylsulfone are stirred in 20 ml of semi-concentrated hydrochloric acid for about 5 minutes over a steam bath until a clear solution is obtained. Then it is poured onto 50 ml of water, made basic with 2N sodium hydroxide solution and the precipitate obtained is suction filtered. This is taken up in dichloromethane. The solution is dried with magnesium sulphate, concentrated to dryness in vacuo and the residue is triturated with ether.

Yellowish crystals; M.p.: 133-135°C.

Example 24

4'-Amino-4-ethylamino-2-cyano-diphenylsulfone

a) 4'-Acetamino-4-amino-2-methoxycarbonyl-diphenylsulfone

Prepared from 4'-acetamino-2-methoxycarbonyl-4-nitro-diphenylsulfone (Lit: J. Med. Chem. 1971, 1168) by catalytic hydrogenation analogously to Example 23b.

Spectra: IR (KBr): 3360, 3450 cm^{-1} NH_2
 1735 cm^{-1} ester-CO
 1650, 1680, 1550 cm^{-1} amide-CO
 UV (methanol): 257 nm and 240 nm.

b) 4'-Acetamino-4-ethylamino-2-methoxycarbonyl-diphenylsulfone

Prepared from 4'-acetamino-4-amino-2-methoxycarbonyl-diphenylsulfone, acetaldehyde and catalytically activated hydrogen analogously to Example 23c.

Amorphous product.

Spectra: IR (CH_2Cl_2): 3440 cm^{-1} -NH
 1740 cm^{-1} ester-CO
 1710, 1520 cm^{-1} amide-CO
 UV (methanol): 260nm, 300nm.

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c) 4-Ethylamino-4'-amino-2-methoxycarbonyl-diphenyl-sulfone

Prepared from 4'-acetamino-4-ethylamino-2-methoxycarbonyl-diphenylsulfone and hydrochloric acid analogously to Example 23d.

M.p.: 155-156°C.

d) 4-Ethylamino-4'-amino-2-carboxy-diphenylsulfone

39 g (0.116 Mol) of 4-ethylamino-4'-amino-2-methoxycarbonyl-diphenylsulfone are refluxed for 4 hours with 10 g of sodium hydroxide in a mixture of 70 ml of water and 350 ml of methanol. After cooling, the mixture is suction filtered to remove a small quantity of an insoluble material; the filtrate is adjusted to pH 4 with hydrochloric acid whereupon the reaction product is precipitated in the form of crystals. These are suction filtered, washed with ice water and dried.

M.p: 116-122°C (decomp.).

e) 4-Ethylamino-4'-amino-2-cyano-diphenylsulfone

37 g (0.115 Mol) of 4-ethylamino-4'-amino-2-carboxy-diphenylsulfone are refluxed for 45 minutes in 370 ml of thionyl chloride. The mixture is concentrated to dryness in vacuo and the residue is carefully mixed with cold concentrated aqueous ammonia. 4-Ethylamino-4'-amino-2-carbamoyl-diphenyl-sulfone is obtained, which is suction filtered, washed with water, dried and dehydrated without any further purification with thionyl chloride to give the nitrile. 32 g (about 0.1 Mol) of the above amide in 220 ml of thionyl chloride are refluxed for 2.75 hours. The reaction mixture is evaporated in vacuo and the crude product is purified by repeated chromatography on silica gel (eluant: methylene chloride/methanol = 40:1).

M.p.: 177-183°C.

Example 25

4'-Amino-2-methyl-4-n-propylamino-diphenylsulfone

a) 2-Methyl-4'-nitro-4-(N-n-propyl-N-tosyl-amino)-diphenylsulfone

2.5 g of 2-methyl-4'-nitro-4-tosylamino-diphenylsulfone, 0.8 ml of n-propyl iodide and 0.9 g of anhydrous potassium carbonate are heated to 60°C for 17 hours in 30 ml of dimethylformamide with stirring. After cooling, the mixture is poured onto water. The solids precipitated are taken up in methylene chloride. The methylene chloride phase is separated, washed with water, dried over sodium sulphate and concentrated to dryness. When the residue is recrystallised from petroleum ether/ethylacetate, yellow crystals are obtained: M.p. 132-135°C.

b) 2-Methyl-4'-nitro-4-n-propylamino-diphenylsulfone

A solution of 2.48 g of 2-methyl-4'-nitro-4-(N-n-propyl-N-tosyl-amino)-diphenylsulfone is left to stand for 4 hours at ambient temperature in 25 ml of concentrated sulfuric acid. Then it is poured into ice/concentrated ammonium hydroxide solution and the solids precipitated are extracted with methylene chloride. The methylene chloride phase is washed with water, dried over sodium sulphate and concentrated to dryness in vacuo and in this way the desired compound is obtained in the form of a yellow solid.

c) 4'-Amino-2-methyl-4-n-propylamino-diphenylsulfone

1.6 g of 2-methyl-4'-nitro-4-n-propylamino-diphenylsulfone are dissolved in 60 ml of methanol and hydrogenated at ambient temperature in the presence of 0.5 g of 10% palladium/charcoal under a hydrogen pressure of 50 psi. After the uptake

of hydrogen has ended (15 minutes) the catalyst is filtered off and the methanolic solution is concentrated to about 10 ml. The colourless crystals precipitated, M.p. 170-173°C, are suction filtered.

Example 26

4'-Amino-4-cyclohexylamino-2-methyl-diphenylsulfone

a) 4-Cyclohexylamino-2-methyl-4'-nitro-diphenylsulfone

2 g of 4-amino-2-methyl-4'-nitro-diphenylsulfone are dissolved in 120 ml of methylene chloride. 15 g of molecular sieve A4 and 2 ml of ethereal hydrochloric acid are added to this solution and then 2 ml of cyclohexanone and 1 g of sodium cyanoborohydride are added with stirring. The mixture is left to stand overnight at ambient temperature and filtered. The filtrate is stirred with 50 ml of 2N hydrochloric acid and then with 200 ml of 2N ammonia for 10 minutes. The methylene chloride phase is removed, washed with water, dried over sodium sulphate and concentrated. The solid yellow residue is chromatographed on silica gel using methylene chloride as eluant. The eluants containing the substance are evaporated and when the residue is recrystallised from ether/petroleum ether, yellow crystals are obtained, M.p. 116-119°C.

b) 4'-Amino-4-cyclohexylamino-2-methyl-diphenyl-sulfone

Prepared from 4-cyclohexylamino-2-methyl-4'-nitro-diphenylsulfone with hydrogen and palladium/-charcoal analogously to Example 25c.

M.p.: 180-183°C.

Example 27

4'-Amino-2-methyl-4-n-propylamino-diphenylsulfone

1.5 g of 2-methyl-4'-nitro-4-propylidenamino-diphenylsulfone (prepared from 4-amino-2-methyl-

4'-nitro-diphenylsulfone, propionaldehyde, titanium(IV) chloride and potassium carbonate in dichloromethane) are dissolved in 50 ml of methanol and hydrogenated in the presence of 0.5 g of palladium/charcoal at ambient temperature under a hydrogen pressure of 50 psi until the uptake of hydrogen has ended. After the catalyst is removed, the remaining mother liquor is concentrated to dryness in vacuo. The residue is chromatographed over silica gel with methylene chloride as the eluant. When the eluants containing the substance are evaporated, colourless crystals are obtained, M.p. 170-173°C.

Example 28

4'-Amino-2-methyl-4-methylamino-diphenylsulfone

Prepared from 2-methyl-4-methylamino-4'-nitro-diphenylsulfone with hydrogen and palladium/charcoal analogously to Example 25c.

M.p.: 150-153°C.

Example 29

4-Ethylamino-4'-amino-2-methyl-diphenylsulfone

Prepared from 4-ethylamino-2-methyl-4'-nitro-diphenylsulfone with hydrogen and palladium/charcoal analogously to Example 25c.

M.p.: 166-167°C.

Example 30

4'-Amino-4-isopropylamino-2-methyl-diphenylsulfone

Prepared from 4-isopropylamino-2-methyl-4'-nitro-diphenylsulfone with hydrogen and palladium/charcoal analogously to Example 25c.

M.p.: 149-150°C.

Example 31

4'-Amino-4-n-hexylamino-2-methyl-diphenylsulfone

Prepared from 4-n-hexylamino-2-methyl-4'-

nitro-diphenylsulfone with hydrogen and palladium/
charcoal analogously to Example 25c.

M.p.: 116-118°C.

Example 32

4'-Amino-4-cyclopentylamino-2-methyl-diphenylsulfone

Prepared from 4-cyclopentylamino-2-methyl-4'-
nitro-diphenylsulfone with hydrogen and palladium/
charcoal analogously to Example 25c.

M.p.: 176-178°C.

Example 33

4'-Amino-4-dimethylamino-2-methyl-diphenylsulfone

Prepared from 4-dimethylamino-2-methyl-4'-
nitro-diphenylsulfone with hydrogen and palladium/
charcoal analogously to Example 25c.

M.p.: 221-223°C.

Example 34

4'-Amino-4-n-hexylamino-2-methyl-diphenylsulfone

Prepared from 4'-acetamino-4-(N-n-hexyl-N-
tosyl-amino)-2-methyl-diphenylsulfone with phenol
and hydrobromic acid analogously to Example 6.

M.p.: 116-118°C.

Example 35

4'-Amino-4-isopropylamino-2-methyl-diphenylsulfone

Prepared from 4'-acetamino-4-(N-isopropyl-
tosyl-amino)-2-methyl-diphenylsulfone with phenol
and hydrobromic acid analogously to Example 6.

M.p.: 149-150°C.

Example 36

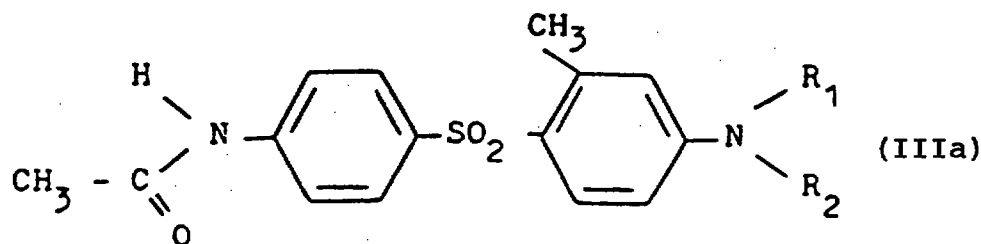
4'-Amino-2-chloro-4-cyclohexylamino-diphenylsulfone

Prepared from 4'-acetamino-2-chloro-4-cyclohexyl-
amino-diphenylsulfone and 3N hydrochloric acid analogously
to Example 22c.

M.p.: 197-199°C.

Example 37

By hydrolysis of a corresponding compound of general formula



the following compounds are obtained analogously to Example 22c:

$ \begin{array}{c} R_1 \\ \diagup \\ -N \\ \diagdown \\ R_2 \end{array} $	Melting point
NHCH ₃	150-153°
NHC ₂ H ₅	166-167°
NHC ₃ H ₇	170-173°
NH-isoC ₃ H ₇	149-150°
NH-C ₆ H ₁₃	116-118°
NH-Cyclopentyl	176-178°
NH-Cyclohexyl	180-183°
N(CH ₃) ₂	221-223°

Example 38

4-Ethylamino-4'-amino-2-hydroxymethyl-diphenylsulfone

Prepared from 4-ethylamino-4'-amino-2-methoxycarbonyl-diphenylsulfone and lithium aluminium hydride analogously to Example 17.

M.p.: 148-151°C.

Example 39

4'-Amino-2-methylamino-4-n-propylamino-diphenylsulfone

Prepared from 4'-acetamino-2-methylamino-4-n-propylamino-diphenylsulfone and 20% hydrochloric acid analogously to Example 22c.

M.p.: 142-143°C

Example 40

4'-Amino-2-methyl-4-n-propylamino-diphenylsulfone

0.8 g of 4'-amino-2-methyl-4-propionylamido-diphenylsulfone are dissolved in 30 ml of dry tetrahydrofuran. The solution obtained is added dropwise with stirring to a suspension of 0.56 g of lithium aluminium hydride in 20 ml of dry tetrahydrofuran at 0°C. After refluxing for two hours, the excess lithium aluminium hydride is destroyed by addition of water after cooling. Subsequently, 0.5 ml of 10 N NaOH is added and the precipitate is removed by suction filtering over kieselgur. After washing of the filtered precipitate with tetrahydrofuran, the filtrate is dried over sodium sulfate and evaporated in vacuo.

M.p.: 170-173°C (ethanol)

Example I

Tablets containing 100 mg of 4,4'-diamino-2-cyano-
diphenylsulfone

Composition:

1 Tablet contains:

Active substance	100.0 mg
Corn starch, suitable for making directly into tablets	60.0 mg
Lactose, suitable for making directly into tablets	38.0 mg
Magnesium stearate	<u>2.0 mg</u>
	200.0 mg

Preparation:

The substances are evenly mixed and compressed
to form tablets.

Example II

Tablets containing 200 mg of 4,4'-diamino-2-cyano-
diphenylsulfone

1 Tablet contains:

Active substance	200.0 mg
Corn starch, suitable for making directly into tablets	120.0 mg
Lactose, suitable for making directly into tablets	76.0 mg
Magnesium stearate	<u>4.0 mg</u>
	400.0 mg

Preparation:

As in Example I.

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Example III

Coated tablets containing 50 mg of 4,4'-diamino-2-cyano-diphenylsulfone and 6.25 mg of pyrimethamine

1 Tablet core contains:

Active substance	50.0 mg
Pyrimethamine	6.25mg
Corn starch, suitable for making directly into tablets	40.0 mg
Lactose, suitable for making directly into tablets	22.75mg
Magnesium stearate	<u>1.0 mg</u>
	120.0 mg

Preparation:

As in Example I.

Coating:

The cores are coated by known methods with a coating consisting essentially of sugar and talc. 30 mg of coating material are used.

Example IV

Tablets containing 100 mg of 4,4'-diamino-2-cyano-diphenylsulfone and 12.5 mg of pyrimethamine

1 Tablet contains:

Active substance	100.0 mg
Pyrimethamine	12.5 mg
Corn starch, suitable for making directly into tablets	60.0 mg
Lactose, suitable for making directly into tablets	25.5 mg
Magnesium stearate	<u>2.0 mg</u>
	200.0 mg

Preparation:

As in Example I.

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Example V

Ampoules containing 100 mg of 4,4'-diamino-2-cyano-diphenylsulfone (i.m. and s.c. crystal suspension)

1 Ampoule contains:

Active substance	100.0 mg
Sodium chloride	15.0 mg
Doubly distilled water	ad. 3.0 ml

Preparation:

The active substance is finely ground (particle size $< 5 \mu\text{m}$). The substance is homogeneously distributed in the sodium chloride solution. The suspension is transferred into 3 ml ampoules and sterilised for 20 minutes at 121°C .

Example VI

Ampoules containing 100 mg of 4,4'-diamino-2-cyano-diphenylsulfone (i.m. and s.c. crystal suspension) and 12.5 mg of pyrimethamine (combination with pyrimethamine)

1 Ampoule contains:

Active substance	100.0 mg
Pyrimethamine	12.5 mg
Sodium chloride	15.0 mg
Doubly distilled water	ad. 3.0 ml

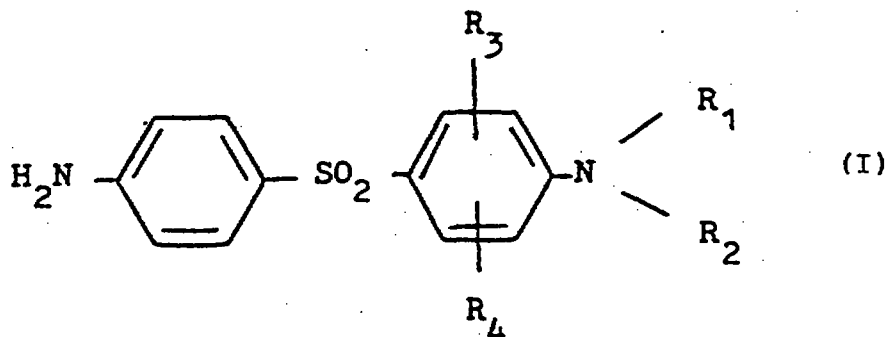
Preparation:

The active substance are finely ground (particle size $< 5 \mu\text{m}$). The substances are homogeneously distributed in the sodium chloride solution. The suspension is transferred into 3 ml ampoules and sterilised for 20 minutes at 121°C .

Patent claims

(150)

1. New substituted bis(4-aminophenyl)-sulfones of general formula



wherein

R_1 represents a hydrogen atom, an alkyl group with 1 to 7 carbon atoms or a cycloalkyl group with 3 to 7 carbon atoms,

R_2 represents a hydrogen atom or an alkyl group with 1 to 3 carbon atoms,

R_3 represents a nitrile, alkylaminocarbonyl, dialkylaminocarbonyl, N-cycloalkyl-alkylaminocarbonyl, alkylamino, dialkylamino, dialkylaminocarbonylalkoxy, alkylaminosulfonyl, dialkylaminosulfonyl, hydroxyalkyl, alkylcarbonyl, aminoalkyl or alkoxyalkyl group

or, if R_1 and R_2 represent hydrogen atoms, a hydroxy or hydroxycarbonylalkoxy group

or, if R_1 represents an alkyl or cycloalkyl group and R_2 represents a hydrogen atom or an alkyl group, it may also represent a halogen atom or a trifluoromethyl, nitro, amino, aminosulfonyl, aminocarbonyl, alkyl, carboxy or alkoxy carbonyl group and



(151)

R_4 represents a hydrogen atom or, if R_1 and R_2 both represent hydrogen atoms and R_3 in the 2 position represents a halogen atom or a hydroxy group, R_4 may also represent a halogen atom or a hydroxy or alkoxy group, whilst the alkyl parts mentioned in the definitions of the groups R_3 and R_4 hereinbefore may each contain 1 to 3 carbon atoms and the cycloalkyl part may contain from 3 to 7 carbon atoms, and the acid addition salts thereof.

2. New compounds of general formula I as claimed in claim 1, wherein

R_1 represents a hydrogen atom, an alkyl group containing 1 to 7 carbon atoms or a cycloalkyl group containing 4 to 7 carbon atoms,

R_2 represents a hydrogen atom or a methyl group,

R_3 represents a nitrile, methylaminocarbonyl, N-cyclohexyl-methylaminocarbonyl, methylamino, dimethyl-amino, dimethylaminocarbonylmethoxy, hydroxymethyl, hydroxyethyl, methylcarbonyl, aminocarbonyl or methoxymethyl group

or, if R_1 and R_2 both represent hydrogen atoms, R_3 may also represent a hydroxy or hydroxycarbonylmethoxy group

or, if R_1 represents an alkyl or cycloalkyl group and R_2 represents a hydrogen atom or a methyl group, R_3 may also represent a chlorine or bromine atom or a methyl, trifluoromethyl, nitro, amino or aminocarbonyl group and

R_4 represents a hydrogen atom or, if R_1 and R_2



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both represent hydrogen atoms and R_3 in the 2 position represents a hydroxy group or a chlorine or bromine atom, R_4 may also represent a chlorine or bromine atom or a hydroxy or methoxy group, and the acid addition salts thereof.

3. New compounds of of general formula I as claimed in claim 1, wherein

R_1 represents a hydrogen atom, an alkyl group with 1 to 3 carbon atoms or a cycloalkyl group with 4 to 7 carbon atoms,

R_2 represents a hydrogen atom or, if R_1 represents a methyl group, R_2 may also represent a methyl group,

R_3 in the 2 position represents a chlorine or bromine atom or a methyl, trifluoromethyl, hydroxymethyl, hydroxyethyl, methylamino, dimethylamino, cyano or methylcarbonyl group and

R_4 represents a hydrogen atom, and the acid addition salts thereof.

4. 4'-Amino-2-methyl-4-n-propylamino-diphenylsulfone and the acid addition salts thereof.

5. 4-Ethylamino-4'-amino-2-chloro-diphenylsulfone and the acid addition salts thereof.

6. Physiologically acceptable acid addition salts of the compounds as claimed in claims 1 to 5 with inorganic or organic acids.

7. Pharmaceutical compositions containing a compound as claimed in claims 1 to 5 or a physiologically



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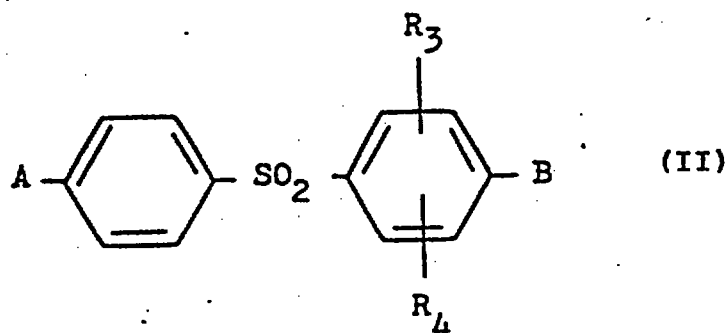
acceptable acid addition salt as claimed in claim 6 together with one or more inert carriers and/or diluents.

8. A compound as claimed in claims 1 to 5 or a physiologically acceptable acid addition salt thereof as claimed in claim 6 for the treatment of bacterial diseases, malaria and leprosy.

9. Process for preparing a pharmaceutical composition for treating bacterial diseases, malaria and leprosy, characterised in that a compound as claimed in claims 1 to 5 or a physiologically acceptable acid addition salt thereof as claimed in claim 6 is incorporated in a non-chemical manner in one or more inert conventional carriers and/or diluents.

10. Process for preparing the compounds as claimed in claims 1 to 6, characterised in that

a) a compound of general formula



wherein

R_3 and R_4 are as defined as in claims 1 to 5,

one of the groups A or B represents a nitro group and the other group A or B represents a

$\begin{matrix} R_1 \\ \diagdown \\ N \\ \diagup \\ R_2 \end{matrix}$ group, wherein R_1 and R_2 are defined a

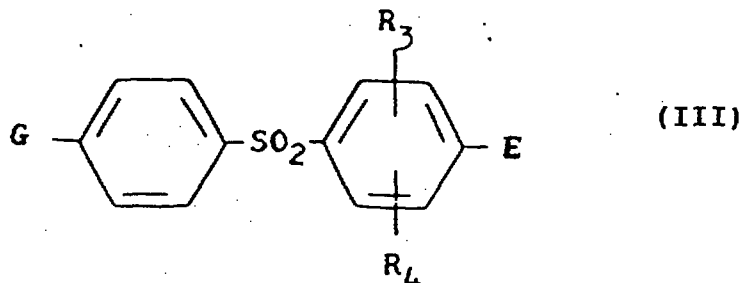
as in claims 1 to 5, or also represents a nitro



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group, is reduced, or

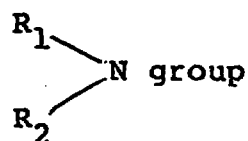
b) one or two protecting groups are split off from a compound of general formula



wherein

R_3 and R_4 are as defined as in claims 1 to 5,

E represents an amino, alkylamino or cycloalkyl-amino group protected by a protecting group, whilst the alkyl part may contain from 1 to 7 carbon atoms and the cycloalkyl part may contain from 3 to 7 carbon atoms, or a



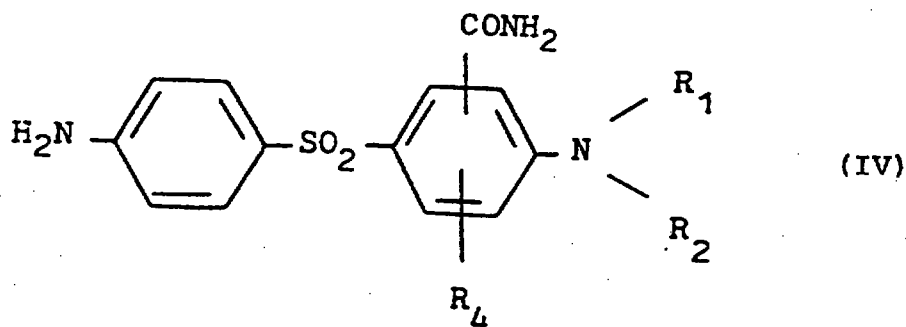
wherein R_1 and R_2 are as defined as in claims 1 to 5, and

G represents an amino group optionally protected by a protecting group, but at least one of the groups E or G must represent one of the above-mentioned groups protected by a protecting group, or

c) in order to prepare compounds of general formula I wherein R_3 represents a cyano group, a compound of general formula

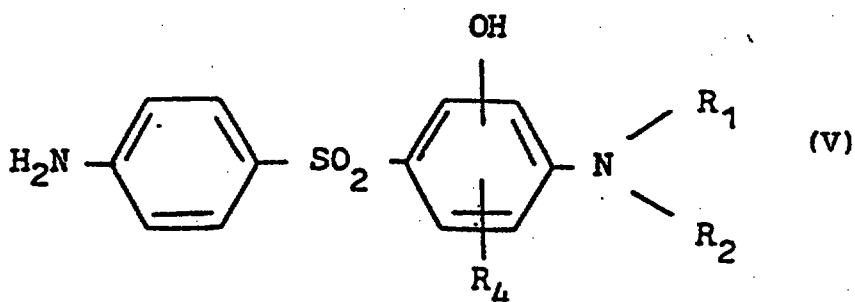


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wherein R_1 , R_2 and R_4 are defined as in claims 1 to 5, is dehydrated, or

d) in order to prepare compounds of general formula I wherein R_3 represents a hydroxycarbonylalkoxy or dialkylaminocarbonylalkoxy group, a compound of general formula



(wherein R_1 , R_2 and R_4 are defined as in claims 1 to 5) is alkylated with a compound of general formula



(wherein Alk represents an alkylene group with 1 to 3 carbon atoms,

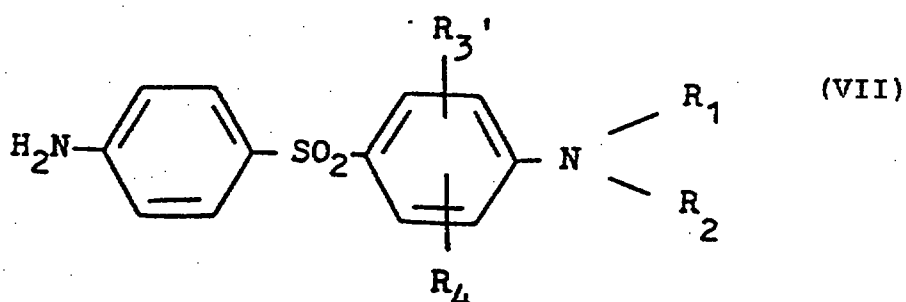
R_5 represents a hydroxy, alkoxy or dialkylamino group, wherein the alkyl part may contain 1 to 3 carbon atoms, and



(15)

X represents a nucleophilically exchangeable group such as a chlorine or bromine atom) and subsequently, if desired, hydrolysed, or

e) in order to prepare compounds of general formula I wherein R_3 represents an aminocarbonyl, alkylamino-carbonyl, dialkylaminocarbonyl or dialkylaminocarbonyl-alkoxy group, a compound of general formula



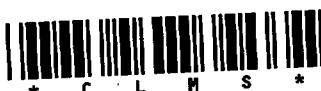
(wherein R_1 , R_2 and R_4 are defined as in claims 1 to 5 and R_3' represents a hydroxycarbonyl or hydroxycarbonyl-alkoxy group), or a reactive derivative thereof, is reacted with an amine of general formula



wherein R_6 represents a hydrogen atom or an alkyl group with 1 to 3 carbon atoms and

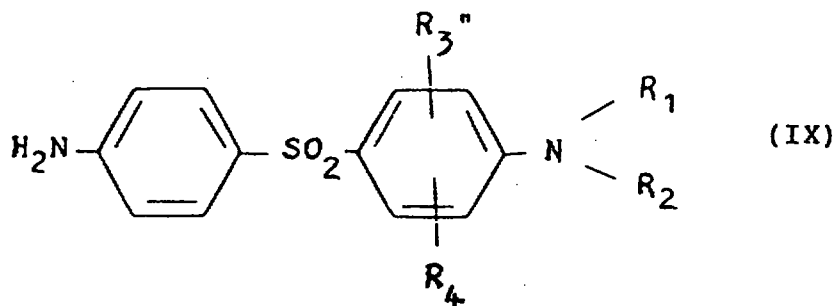
R_7 represents a hydrogen atom or an alkyl group with 1 to 3 carbon atoms, or the reactive derivatives thereof, or

f) in order to prepare compounds of general formula I wherein R_3 represents a hydroxymethyl,



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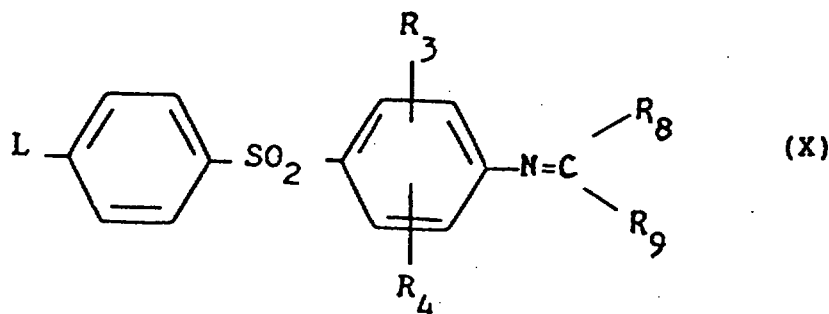
aminomethyl or 1-hydroxyalkyl group, a compound of general formula



wherein R_1 , R_2 and R_4 are defined as in claims 1 to 5 and

R_3'' represents a hydroxycarbonyl, alkoxycarbonyl, aminocarbonyl or alkylcarbonyl group, wherein the alkylcarbonyl group may contain a total of 2 to 4 carbon atoms, is reduced, or

g) in order to prepare compounds of general formula I wherein R_1 represents an alkyl or cycloalkyl group and R_2 represents a hydrogen atom, a compound of general formula



wherein R_3 and R_4 are defined as in claims 1 to 5,

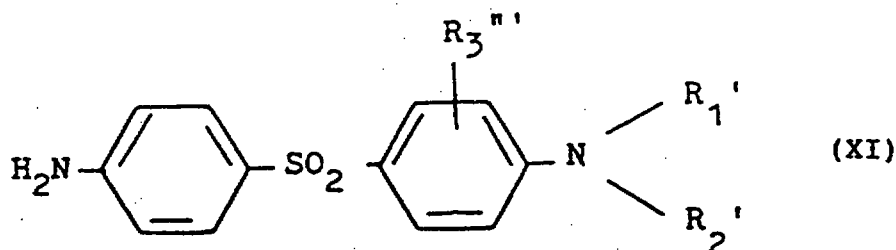
L represents an amino or nitro group and

R_8 and R_9 together with the carbon atom between them represent an alkylidene group with 1 to 7



carbon atoms or a cycloalkylidene group with 3 to 7 carbon atoms, is reduced, or

h) in order to prepare compounds of general formula I wherein at least one of the groups R_1 or R_2 does not represent a hydrogen atom and R_3 represents a halogen atom or an alkylamino, dialkylamino, hydroxyalkyl, aminoalkyl, alkoxyalkyl, hydroxy, amino, trifluoromethyl or alkyl group, a compound of general formula



wherein R_1' and R_2' have the meanings given for R_1 and R_2 in claims 1 to 5, but one of the groups R_1' or R_2' must represent an alkanoyl group with 1 to 7 carbon atoms, and

R_3''' represents a halogen atom or an alkylamino, dialkylamino, hydroxyalkyl, aminoalkyl, alkoxyalkyl, hydroxy, amino, trifluoromethyl or alkyl group, whilst the alkyl part may contain 1 to 3 carbon atoms, is reduced, and

if desired a compound of general formula I thus obtained wherein R_3 represents an alkoxy carbonyl or alkoxy carbonyl-alkoxy group is converted by hydrolysis into a corresponding compound of general formula I wherein R_3 represents a hydroxy carbonyl or hydroxy carbonyl-alkoxy group,

or a compound of general formula I thus obtained wherein R_3 and/or R_4 represent a chlorine



or bromine atom is converted by hydrolysis or alcoholysis into a corresponding compound of general formula I wherein R_3 in the 2-position represents a hydroxy or alkoxy group and R_4 represents a chlorine or bromine atom, or

a compound of general formula I thus obtained is converted into an acid addition salt thereof, more particularly a physiologically acceptable acid addition salt, with inorganic or organic acids.

11. Pharmaceutical compositions containing a compound as claimed in claims 1 to 5 or a physiologically acceptable acid addition salt as claimed in claim 6 and a dihydrofolic acid reductase inhibitor together with one or more inert carriers and/or diluents.

12. Process for preparing a pharmaceutical compositions for the treatment of bacterial diseases, malaria and leprosy, characterised in that a compound as claimed in claims 1 to 5 or a physiologically acceptable acid addition salt thereof as claimed in claim 6 and a dihydrofolic acid-reductase inhibitor is incorporated, by a non-chemical method, in one or more inert conventional carriers and/or diluents.

