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PATENT SPECIFICATION

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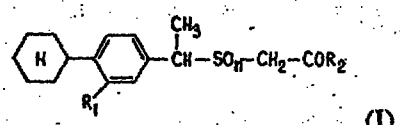
(54) SULFIDES, SULFOXIDES AND SULFONES

(71) We, DR. KARL THOMAE GESELLSCHAFT MIT BESCHRANKTER HAFTUNG, a Body Corporate organised under the laws of the Federal Republic of Germany of Biberach an der Riss, Federal Republic of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new cyclohexylphenyl derivatives, to processes for their preparation and to pharmaceutical compositions containing them.

According to one feature of the present invention there are provided compounds of general formula I,



(I)

wherein

R_1 represents a hydrogen or halogen atom;
R_2 represents a hydroxy group, an alkoxy group containing from 1 to 6 carbon atoms, an aralkoxy group containing from 7 to 10 carbon atoms, an amino group (optionally substituted by an alkyl group containing from 1 to 3 carbon atoms), a piperidino group or a morpholino group; and

n is 0, 1 or 2;

and, where R_2 represents a hydroxy group, the salts thereof.

The compound according to the invention possess interesting pharmacological properties and in particular, in general, an antithrombotic activity, a prolongation activity on the bleeding time and a lowering activity on body cholesterol and triglyceride levels.

It will be appreciated that, for pharmaceutical use, the salts of the compounds of general formula I wherein R_2 represents a hydroxy group referred to above will be physiologically compatible salts but other salts may find use, for example, in the preparation of compounds of general formula I and, wherein R_2—represents a hydroxy group, their physiologically compatible salts.

It will be further appreciated that the compounds according to the invention may exist in the form of optically active isomers. The present invention includes within its scope the compounds in the form of optically active isomers as well as isomeric mixtures thereof.

In the compounds according to the invention R_1 preferably represents a hydrogen or chlorine atom. Also preferred is that R_2 represents a hydroxy, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isoamyloxy, hexyloxy, benzyloxy, amino, isopropylamino, piperidino or morpholino group.

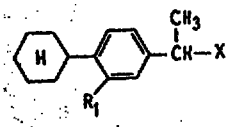
Particularly preferred compounds according to the invention are the following:

[1 - (4 - Cyclohexylphenyl) - ethylsulfinyl] - acetic acid and salts thereof
Methyl [1 - (4 - cyclohexylphenyl) - ethylsulfinyl] acetate
Methyl [1 - (3 - chloro - 4 - cyclohexyl - phenyl) - ethylsulfinyl] acetate
Ethyl [1 - (3 - chloro - 4 - cyclohexyl - phenyl) - ethylsulfinyl] acetate
[1 - (3 - Chloro - 4 - cyclohexyl - phenyl) - ethylsulfinyl] acetic acid piperidide and salts thereof.

The compounds of general formula I may for example, be prepared according to the following processes which processes constitute further features of the present invention:

a) For the preparation of compounds of general formula I wherein n is 0:

Reaction of a compound of formula II,



(II)

(wherein R_1 is as hereinbefore defined and X represents a hydroxy group or a halogen atom) with a compound of formula III,

$$HS—CH_2—COR_2 \qquad (III)$$

(wherein R_2 is as hereinbefore defined).

The reaction is preferably carried out in dimethylsulfoxide as solvent. Optionally the reaction may be effected in the presence of a base such as for example, potassium carbonate, triethylamine or pyridine or, when X represents a hydroxy group, in the presence of an acid such as for example hydrochloric acid or sulfuric acid. Preferred reaction temperatures are from 0 to 100°C, particularly preferred being temperatures of from 5 to 30°C.

When, in the compound of formula III, R_2 represents an alkoxy or aralkoxy group then, depending on the reaction conditions employed, this group may be converted into a hydroxy group during the reaction.

b) For the preparation of compounds of general formula I wherein n is 1 or 2:

Oxidation of a compound of formula I as hereinbefore (wherein n is less than the value of n in the desired compound of formula I) whereby the desired compound of formula I is obtained.

The oxidation is preferably carried out in the presence of a solvent, e.g. water, aqueous pyridine, acetone, glacial acetic acid, dilute sulfuric acid or trifluoro acetic acid. Preferred temperatures are from −80 to 100°C depending on the agent employed to effect oxidation.

Compounds of general formula I wherein n is 1 may be formed by oxidation of a compound of formula 1 wherein n is 0, preferably by reaction with a substantially equimolar quantity of an oxidising agent. Suitable oxidising agents include, for example, hydrogen peroxide used preferably either in the presence of glacial acetic acid and at 0 to 20°C or in acetone and at 0 to 60°C; a peracid, such as e.g. performic acid, used preferably in the presence of glacial acetic acid or trifluoroacetic acid and at 0 to 50°C; sodium metaperiodate used preferably in the presence of aqueous methanol or ethanol and at 15 to 25°C; tert. - butyl hypochlorite used preferably in the presence of methanol and at −80 to −30°C; iodobenzene dichloride used preferably in the presence of aqueous pyridine and at 0 to 5°C; nitric acid used preferably in the presence of glacial acetic acid and at 0 to 20°C; and chromic acid used preferably either in the presence of glacial acetic acid or acetone and at 0 to 20°C.

Compounds of general formula I wherein n is 2 may be prepared either by oxidation of a compound of formula I wherein n is 1 in which case oxidation is preferably effected by reaction with a substantially equimolar quantity of an oxidising agent or by oxidation of a compound of formula I wherein n is 0, in which case oxidation is preferably effected by reaction of the compound of formula I with an oxidising agent in a molar ratio of substantially 1:2.

In either case suitable oxidising agents include, for example, hydrogen peroxide used preferably either in the presence of glacial acetic acid and at 20 to 100°C or in the presence of acetone and at 0 to 60°C; a peracid such as e.g. performic acid or *m* - chloroperbenzoic acid used preferably in the presence of glacial acetic acid, trifluoroacetic acid or chloroform and at temperatures of from 0 to 50°C; nitric acid used preferably in the presence of glacial acetic acid and at 0 to 20°C; and chromic acid and potassium permanganate used preferably in the presence of glacial acetic acid, acetone or aqueous sulfuric acid and at 0 to 20°C.

c) For the preparation of compounds of general formula I wherein R_2 is other than a hydroxy group:

Reaction of a compound of general formula I as hereinbefore defined (wherein R_2 represents a hydroxy group) or an acid halide or anhydride thereof with a compound of formula IV,

$$R_2'—Y \qquad (IV)$$

(wherein R_2' represents an alkyl group containing from 1 to 6 carbon atoms, an aralkyl group containing from 7 to 10 carbon atoms, an amino group (optionally substituted by an alkyl group containing from 1 to 3 carbon atoms), a piperidino or morpholino group and Y represents a hydroxy group, a chlorine, bromine or iodine atom, a sulfate or phosphate group or may, when R_2' represents an amino group (optionally substituted by an alkyl group containing from 1 to 3 carbon atoms), a piperidino or morpholino group, represent a hydrogen atom.

The reaction is preferably carried out in the presence of ether, chloroform, benzene, tetrahydrofuran, dioxan, dimethylformamide, dimethylsulfoxide, hexamethylphosphoric acid triamide or an excess of the compound of formula IV as solvent and optionally in the presence of an acid activating agent, a dehydrating agent and/or a base. Preferred reaction temperatures are from −20 to 150°C.

When, in the compound of formula IV, Y represents a hydroxy group, i.e. when the compound of formula IV is an alcohol such as, for example, methanol, ethanol, propanol, iso-

propanol, butanol, isoamylalcohol, hexanol or benzyl alcohol, the reaction is preferably carried out in the presence of an acid such as, for example, sulfuric acid, *p* - toluenesulfonic acid or hydrochloric acid. Also preferred is the presence of phosphorus oxychloride, thionyl chloride or chlorosulfonic acid as an acid activating agent; cyclohexylcarbodiimide, carbonyl diimidazole or 2,2 - dimethoxypropane as a dehydrating agent; and/or a corresponding chloroformic acid ester. The reaction may also optionally be carried out in the presence of a base such as, for example, potassium carbonate or triethylamine. Preferred reaction temperatures are from 20 to 100°C.

When the compound of formula IV is a sulfate such as e.g. dimethyl sulphate, a phosphate such as e.g. triethyl phosphate or a halide such as e.g. methyl iodide, ethyl iodide or propyl iodide, i.e. when, in the compound of formula IV, Y represents a sulfate or phosphate group or a chlorine, bromine or iodine atom, the reaction is preferably carried out in the presence of a dipolar aprotic solvent. It is also preferred that the reaction is effected in the presence of potassium carbonate, calcium hydroxide or sodium hydroxide as a base. Preferred reaction temperatures are from 20 to 80°C. The reaction may also, however, be carried out as a phase transfer-catalyzed two-phase reaction, for example in the presence of chloroform and water and optionally in the presence of quaternary ammonium salts such as e.g. tetrabutylammonium iodide.

When the compound of formula IV is an amine such as e.g. ammonia, isopropylamine, piperidine or morpholine, i.e. when Y represents a hydrogen atom, the reaction is preferably carried out in the presence of cyclohexylcarbodiimide or carbonyl diimidazole as a dehydrating agent and in the presence of dioxan or tetrahydrofuran as solvent. Preferred reaction temperatures are from 10 to 50°C.

d) For the preparation of a compound of general formula I wherein R_2 represents a hydroxy group:

Hydrolysis of a compound of formula I as hereinbefore defined (wherein R_2 is other than a hydroxy group).

The compounds of general formula I wherein R_2 represents a hydroxy group may, if desired, be converted into their physiologically compatible salts by reaction with an appropriate inorganic or organic base. Suitable bases include, for example, sodium hydroxide, potassium hydroxide and cyclohexylamine.

The compound according to the invention may be obtained in the form of their optically active isomers by separation of an isomeric mixture thereof, suitable separation techniques being well known in the art.

The compounds of general formulae II to VI, used as starting compounds in the processes according to the invention may be obtained according to methods known from the literature. Methods for the preparation of these compounds are illustrated hereinafter in the Examples.

As mentioned above, the compounds according to the invention possess interesting pharmacological properties. Those compounds which we have tested have exhibit an inhibitory activity on thrombocyte aggregation, a prolongation activity on the bleeding time and a lowering activity on body cholesterol and triglyceride levels.

These compounds are thus useful in the prophylactic treatment of arterial thromboembolism and diseases of arterial occlusion.

For example the following compounds have been tested with regard to their pharmacological activities:

A=[1 - (4 - Cyclohexylphenyl) - ethylsulfinyl]acetic acid (M.p.: 152—154°C)

B=Methyl [1 - (4 - cyclohexylphenyl) - ethylsulfinyl]acetate (M.p.: 113—115°C)

C=Methyl [1 - (3 - chloro - 4 - cyclohexyl - phenyl) - ethylsulfinyl]acetate (M.p.: 93—95°C)

D=Methyl [1 - (3 - chloro - 4 - cyclohexyl - phenyl) - ethylsulfinyl]acetate (M.p.: 80—82°C)

E=[1 - (3 - Chloro - 4 - cyclohexyl - phenyl) - ethylsulfinyl]acetic acid piperidide (oil, R_f values of 0.6 and 0.5 under the conditions hereinbefore defined.

1. Determination of platelet aggregation according to the method of Born and Cross (see J. Physiol. *170,* 397 (1964)):

The platelet aggregation was measured in the platelet-rich plasma of healthy human donors. The variation in optical density of a platelet suspension was measured and recorded photometrically after the addition of commercial collagen of Messrs. Hormonchemie, Munich, containing 1 mg of collagen fibrils per ml. From the angle of inclination of the density curve, the velocity of aggregation was estimated (Vmax). The optical density was taken as the point on the curve where the most light was transmitted (O.D.). Small doses of collagen were used, but sufficient to give irreversible aggregation. To provoke maximum aggregation, about 0.01 ml of the collagen solution was added to 1 ml of platelet-rich plasma.

The values in the following table represent the inhibition of the aggregation velocity in % (Vmax) and the change in optical density (O.D.) in % compared with a control group to which the substance under test was not administered.

Compound	Inhibition in % after application of 10^{-4} mol/l Vmax	O.D.
C	85	89
D	87	89
E	90	92

2. Determination of the prolongation of the bleeding time:

To determine the bleeding time, 10 mg/kg of the compound under test were administered orally to mice which had not previously been anaesthetized. After 1 and after 3 hours, about 0.5 mm was cut off from the tail of each animal. A sample of blood was soaked up into filter paper every 30 seconds. The number of drops of blood so obtained acted as a standard for the bleeding time (5 animals/experiment).

The values in the following table represent the prolongation in % compared with a control group:

Compound	Prolongation of the bleeding time in % after 1 hour	3 hours
A	3000	122
B	117	51
D	49	
E	37	

3. Acute toxicity:

The acute toxicity of the compound under test was determined in white mice (observation time: 14 days) after oral administration of a single dose:

Compound	Acute toxicity
A	>1000 mg/kg (0 out of 10 animals died)
B	>1000 mg/kg (0 out of 10 animals died)
E	>1000 mg/kg (0 out of 10 animals died)

According to a still further feature of the present invention there are provided pharmaceutical compositions comprising, as active ingredient, at least one compound of formula I as hereinbefore defined or, where R_2 represents a hydroxy group, a physiologically compatible acid addition salt thereof, in association with a pharmaceutical carrier or excipient.

For pharmaceutical administration the compounds of general formula I and, where R_2 represent a hydroxy group, their physiologically compatible salts may be incorporated into conventional pharmaceutical preparations, optionally in combination with other active ingredients. The compositions may, for example, be presented in a form suitable for oral, rectal or parenteral administration. Thus, for example, compositions for oral administration may be solid or liquid and may take the form of tablets, coated tablets, solutions or suspensions, such compositions comprising carriers or excipients conventionally used in the pharmaceutical art. Thus, for example, suitable tabletting excipients include lactose, corn starch, polyvinyl - pyrrolidone and magnesium stearate. Compositions for rectal administration may, for example, take the form of suppositories, the carrier comprising a suppository base, while compositions for parenteral administration may, for example, be in the form of ampoules, solutions or suspensions.

Advantageously the compositions may be formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredient. Suitable dosage units for adults contain from 10 to 50 mg of active ingredient.

The following non-limiting Examples serve to illustrate the present invention. Examples A and B illustrate the preparation of starting materials.

Preliminary remarks:

For column chromatography silica gel of Messrs. Woelm, grain size 0.05 to 0.2 mm, was used.

For thin-layer chromatography (TLC) the following carriers were used:

A ≙ silica gel—precoated plates SIL G/UV 254 of Messrs. Macherey, Nagel & Co.

B ≙ silica gel—"Merck" [registered Trade Mark] preprepared plate F 254.

Example A

1 - (4 - Cyclohexylphenyl) - 1 - hydroxy - ethane

11.4 g (0.3 mol) of sodium borohydride were added, in small amounts, to 60.7 g (0.3 mol) of 4' - cyclohexyl - acetophenone (m.p.: 66—67°C) in 300 ml of methanol whilst stirring vigorously and cooling with ice at 20—25°C. The mixture obtained was stirred for one hour at room temperature and the product thus formed was precipitated with acidified ice-water. The product was filtered off under suction, washed and dried to yield 62.6 g of crystalline material. A sample was recrystallized from petroleum ether whereupon it melted at 81.5—82.5°C.

$C_{14}H_{20}O$ (204.31)

Calculated: C 82.30 H 9.87

Found: C 82.40 H 9.92

Example B

1 - (4 - Cyclohexylphenyl) - 1 - chloro - ethane

61.3 g of crude 1 - (4 - cyclohexylphenyl) - 1 - hydroxy - ethane were dissolved in 600 ml of benzene and 100 g of dry magnesium sulfate were added thereto. Anhydrous hydrogen chloride gas was introduced at room temperature whilst stirring until TLC of a sample of the reaction mixture (carrier A, cyclohexene - ethyl acetate=4/1) showed the reaction to be

complete. The magnesium sulfate was filtered off under suction and the organic layer was washed with water, dried and evaporated. 68.4 g of an oil were obtained having an R_f value 0.8 (carrier A, cyclohexene - ethyl acetate=4/1).

Analogously were obtained:

1 - (3 - Chloro - 4 - cyclohexyl - phenyl) - 1 - hydroxy - ethane oil, R_f value 0.3 on carrier A with cyclohexane - ethyl acetate=4/1

1 - (3 - Chloro - 4 - cyclohexyl - phenyl) - 1 - chloro - ethane oil, R_f value 0.8 on carrier A with cyclohexane - ethyl acetate=4/1.

Example 1

Methyl [1 - (4 - cyclohexylphenyl) - ethylthio]acetate

50.6 g (0.45 mol) of 1 - (4 - cyclohexylphenyl) - 1 - chloro - ethane and 48 g (0.45 mol) of methyl thioglycolate were dissolved in 300 ml of dimethylsulfoxide and 69 g (0.5 mol) of dry potassium carbonate were added thereto in small amounts at room temperature whilst stirring. The mixture obtained was subsequently stirred for 2 hours and then 600 ml of water were added thereto. The product thus formed was extracted with toluene. After washing, drying and evaporating the extracts, 79 g of an oil were obtained. R_f value: 0.7 (carrier A with cyclohexane - ethyl acetate=4/1).

$C_{17}H_{24}O_2S$ (292.44)
Calculated: C 69.82 H 8.27 S 10.96
Found: C 69.58 H 8.39 S 10.86

Example 2

Methyl [1 - (3 - chloro - 4 - cyclohexyl - phenyl) - ethylthio]acetate

Prepared analogously to Example 1 from 1 - (3 - chloro - 4 - cyclohexyl - phenyl) - 1 - chloro - ethane and methyl thioglycolate. Oil; R_f value: 0.8 (carrier A with cyclohexane - ethyl acetate=4/1.

Yield: 95% of theory.
$C_{17}H_{23}ClO_2S$ (330.89)
Calculated:
C 62.92 H 7.01 Cl 10.72 S 9.69
Found:
C 63.10 H 7.20 Cl 10.60 S 9.85

Example 3

[1 - (4 - Cyclohexylphenyl) - ethylthio]-acetic acid

87.5 g (0.3 mol) of methyl [1 - (4 - cyclohexylphenyl) - ethylthio]acetate were boiled in 300 ml of isopropanol for 1 hour with a solution of 25 g of potassium hydroxide. On subsequent standing the potassium salt of the acid crystallized out and was isolated by filtration under suction and then washed with isopropanol and ether.

Yield: 83.3 (87.8% of theory), m.p. 232—233°C.
$C_{16}H_{21}KO_2S$ (316.50)
Calculated: C 60.70 H 6.69 S 10.13
Found: C 60.40 H 6.88 S 10.10

By acidification of the above-obtained salt the free acid was obtained as an oil. R_f value: 0.6 (carrier A with cyclohexane - ethyl acetate=2/1).

$C_{16}H_{22}O_2S$ (278.42)
Calculated: C 69.03 H 7.97 S 11.52
Found: C 69.00 H 7.95 S 11.27

Example 4

[1 - (3 - Chloro - 4 - cyclohexyl - phenyl) - ethylthio]acetic acid

Prepared analogously to Example 3 from methyl [1 - (3 - chloro - 4 - cyclohexyl - phenyl) - ethylthio]acetate by hydrolysis.

Yield: 84% of theory.
m.p.: 80—82°C (from petroleum ether)

Example 5

[1 - (4 - Cyclohexylphenyl) - ethylthio]-acetic acid

491 g (2.4 mol) of 1 - (4 - cyclohexylphenyl) - 1 - hydroxy - ethane were dissolved in 2.4 ltrs. of toluene and 250 ml (332 g) of 80% thioglycolic acid were added thereto. Whilst cooling with ice-water and stirring vigorously, 220 ml (369 g≙2.4 mol) of phosphorus oxychloride were added dropwise to the mixture thus obtained such that the internal temperature was about 40°C. The reaction mixture was subsequently stirred at room temperature for a further 2 hours and then 2 ltrs. of ice-water were stirred therein. The organic layer was separated, dried and evaporated. 675 g of crude acid were obtained. The acid was dissolved in a solution of 148 g of potassium hydroxide in 1.48 ltrs. of ethanol. On cooling the solution thus formed the potassium salt crystallized out.

When the mother liquor was worked up, the yield was 623 g (82% of theory) of potassium salt with m.p. 232—233°C.

550 g (82% of theory) of the free acid were obtained as an oil by acidification.

Example 6

[1 - (3 - Chloro - 4 - cyclohexyl - phenyl) - ethylthio]acetamide

13.8 g (0.085 mol) of carbonyl diimidazole were added to 17.7 g (0.057 mol) of [1 - (3 - chloro - 4 - cyclohexyl - phenyl)ethylthio]-acetic acid in 200 ml of dry tetrahydrofuran. On cessation of carbon dioxide evolution (about 20 minutes), dry ammonia gas was introduced into the solution of the imid-

azolide. The mixture obatined was allowed to stand overnight and then evaporated *in vacuo*. The residue was distributed between ethyl acetate and dilute hydrochloric acid. After washing and drying 17.5 g of an oil having an R_f value of 0.3 were obtained from the ethyl acetate layer (carrier A with cyclohexane - ethyl acetate=1/1). The oil was subsequently crystallized from cyclohexane.

Yield: 13.4 g (75.8% of theory).
m.p.: 92—94°C
$C_{14}H_{22}ClNOS$ (311.89)
Calculated: Cl 11.37 S 10.28
Found: Cl 11.45 S 10.45

Example 7

[1 - (3 - Chloro - 4 - cyclohexyl - phenyl) - ethylthio]acetic acid piperidide

Prepared analogously to Example 6 from [1 - (3 - chloro - 4 - cyclohexyl - phenyl) - ethylthio]acetic acid, carbonyl diimidazole and piperidine.

Yield: 99% of theory,
oil, R_f value: 0.7 (carrier A with cyclohexane - ethyl acetate=1/1).
$C_{21}H_{30}ClNOS$ (380.00)
Calculated:
C 66.38 H 7.96 Cl 9.33 N 3.69
S 8.44
Found:
C 66.20 H 7.54 Cl 9.18 N 3.85
S 8.18

Example 8

[1 - (3 - Chloro - 4 - cyclohexyl - phenyl) - ethylthio]acetic acid morpholide

Prepared analogously to Example 6 from [1 - (3 - chloro - 4 - cyclohexyl - phenyl) - ethylthio]acetic acid, carbonyl diimidazole and morpholine.

Yield: 95% of theory,
oil, R_f value: 0.5 (carrier A with cyclohexane - ethyl acetate=1/1).
$C_{20}H_{28}ClNO_2S$ (381.975)
Calculated:
C 62.89 H 7.39 Cl 9.28 N 3.67
S 8.39
Found:
C 62.02 H 7.48 Cl 9.14 N 3.92
S 8.60

Example 9

Diastereoisomeric [1 - (4 - cyclohexylphenyl) - ethylsulfinyl] - acetic acids

a) Slightly soluble isomer

61.5 g (0.22 mol) of [1 - (4 - cyclohexylphenyl) - ethylthio] - acetic acid were dissolved in 200 ml of glacial acetic acid and 21.4 g (0.23 mol) of 36.8% perhydrol were added dropwise thereto at 15°C. The mixture obtained was allowed to stand at room temperature for 1½ hours and then the reaction product formed was filtered off under suction and washed with petroleum ether.

Yield: 31.3 g (48.6% of theory),
m.p.: 152—154°C (decomp.).
$C_{16}H_{22}O_3S$ (294.40)
Calculated: C 65.28 H 7.53 S 10.89
Found: C 65.50 H 7.64 S 10.87

Characteristic signals in the NMR spectrum ($CDCl_3$—CD_3OD):
CH_2: singlet at 3.5 ppm
CH: quartet at 4.25 ppm (J=7 Hz)

b) Fairly soluble isomer

The acetate filtrate of the slightly soluble isomer prepared above was evaporated *in vacuo*. The residue (33.1 g) was recrystallized twice from toluene.

Yield: 18.1 g (28.2% of theory),
m.p.: 128—132°C (decomp.).
$C_{16}H_{22}O_3S$ (294.40)
Calculated: C 65.28 H 7.53 S 10.89
Found: C 65.40 H 7.49 S 10.82

Characteristic signals in the NMR spectrum ($CDCl_3$—CD_3OD):
CH_2: doublet at 3.4 ppm (J=8 Hz)
CH: quartet at 4.2 ppm (J=7 Hz).

Example 10

Methyl [1 - (4 - cyclohexylphenyl) - ethylsulfinyl]acetate

2.94 g (10 mmol) of [1 - (4 - cyclohexylphenyl) - ethylsulfinyl] - acetic acid (slightly soluble isomer, m.p.: 152—154°C) were dissolved in 30 ml of benzene and 0.5 g of methanol and then 2.48 g (12 mmol) of dicyclohexylcarbodiimide were added thereto. The mixture obtained was stirred for 1 hour and then 10 ml of 2 N acetic acid were added thereto. The dicyclohexylurea formed was filtered off under suction. 2.4 g (78% of theory) of product were obtained from the organic layer after evaporation and recrystallization from cyclohexane - petroleum ether.

M.p.: 112—114°C.
$C_{17}H_{24}O_3S$ (308.45)
Calculated: C 66.20 H 7.84 S 10.40
Found: C 66.40 H 7.94 S 10.37

Characteristic signals in the NMR spectrum ($CDCl_3$):

CH_2: double doublet at 3.4 ppm (J=14 Hz)
CH: quartet at 4.05 ppm (J=7 Hz, $\delta\gamma$=22 Hz).

Example 11

Methyl [1 - (4 - cyclohexylphenyl) - ethylsulfinyl]acetate

200 g (0.681 mol) of [1 - (4 - cyclohexyl-

phenyl) - ethylsulfinyl]acetic acid (slightly soluble isomer, m.p.: 152—154°C) were dissolved in 680 ml of dimethylsulfoxide and 96.6 g 0.75 mmol) of ethyl - diisopropyl - amine were added thereto whilst cooling. To the mixture obtained were added, dropwise, 106 g (0.75 mol≙46.6 ml) of methyl iodide at 20°C within 20 minutes. The resultant mixture was stirred for a further hour and then the reaction product was precipitated with 2 ltrs. of water. The product was filtered off under suction, dried and recrystallized, first from petroleum ether then from isopropanol.
Yield: 169.5 g=80.7% of theory,
m.p.: 113—115°C (from petroleum ether).

Example 12

Methyl [1 - (4 - cyclohexylphenyl) - ethylsulfinyl]acetate

Prepared analogously to Example 10 from [1 - (4 - cyclohexylphenyl) - ethylsulfinyl]-acetic acid (fairly soluble isomer, m.p.: 128—132°C).

Yield: 71% of theory, m.p.: 81—85°C.

Example 13

Ethyl [1 - (4 - cyclohexylphenyl) - ethylsulfinyl]acetate

Prepared analogously to Example 11 from [1 - (4 - cyclohexylphenyl) - ethylsulfinyl]-acetic acid (m.p.: 152—154°C) and ethyl iodide.

Yield: 68% of theory,
m.p.: 75—77°C (from petroleum ether).
$C_{16}H_{26}O_3S$ (322.47)
Calculated: C 67.03 H 8.14 S 9 .94
Found: C 67.30 H 8.16 S 10.04
NMR spectrum ($CDCl_3$):
CH_2: double doublet at 3.36 ppm (J= 14 Hz, $\delta\nu$=29 Hz).

Example 14

Isopropyl [1 - (4 - cyclohexylphenyl) - ethylsulfinyl]acetate

10.0 g (34 mmol) of [1 - (4 - cyclohexylphenyl) - ethylsulfinyl]acetic acid (m.p.: 152—154°C), dissolved in 50 ml of dry tetrahydrofuran, were mixed with 6.1 g (37.4 mmol) of carbonyl diimidazole. After cessation of carbon dioxide evolution (about 20 minutes), 2.2 g (37 mmol) of isopropanol were added thereto. The mixture obtained was left to react overnight and then evaporated *in vacuo*. The residue was distributed between water and ethyl acetate. After washing with sodium carbonate solution and dilute hydrochloric acid followed by drying, the organic layer was evaporated and the residue was filtered on silica gel with cyclohexane - ethyl acetate=1/4. The eluate was evaporated and the residue was recrystallized from petroleum ether.

Yield: 5.3 g (46% of theory),
m.p.: 95—97°C.
$C_{19}H_{28}O_3S$ (336.60)
Calculated: C 67.82 H 8.39
Found: C 67.90 H 8.39

Example 15

Isobutyl [1 - (4 - cyclohexylphenyl) - ethylsulfinyl]acetate

Prepared analogously to Example 14 from [1 - (4 - cyclohexylphenyl) - ethylsulfinyl]-acetic acid (m.p.: 152—154°C), isobutanol and carbonyl diimidazole.

Yield: 68% of theory,
m.p.: 79—81°C (from petroleum ether).
$C_{20}H_{30}O_3S$ (350.53)
Calculated: C 68.52 H 8.63 S 9.15
Found: C 68.50 H 8.58 S 9.06

Example 16

Isoamyl [1 - (4 - cyclohexylphenyl) - ethylsulfinyl]acetate

Prepared analogously to Example 14 from [1 - (4 - cyclohexylphenyl) - ethylsulfinyl]-acetic acid (m.p.: 152—154°C), isoamyl alcohol and carbonyl diimidazole.

Yield: 75.0% of theory,
m.p.: 69—70° (from petroleum ether).
$C_{21}H_{32}O_3S$ (364.55)
Calculated: C 69.19 H 8.85 S 8.80
Found: C 69.40 H 8.78 S 8.78

Example 17

n - Hexyl [1 - (4 - cyclohexylphenyl) - ethylsulfinyl]acetate

Prepared analogously to Example 14 from [1 - (4 - cyclohexylphenyl) - ethylsulfinyl]-acetic acid (m.p.: 152—154°C), n - hexanol and carbonyl diimidazole.

Yield: 82% of theory,
m.p.: 73—74°C (from petroleum ether)
$C_{22}H_{34}O_3S$ (378.58)
Calculated: C 69.80 H 9.05 S 8.47
Found: C 69.70 H 9.38 S 8.24

Example 18

Benzyl [1 - (4 - cyclohexylphenyl) - ethylsulfinyl]acetate

Prepared analogously to Example 14 from [1 - (4 - cyclohexylphenyl) - ethylsulfinyl]-acetic acid (m.p.: 152—154°C), benzyl alcohol and carbonyl diimidazole.

Yield: 78% of theory,
m.p.: 76—77°C (from cyclohexane - petroleum ether=1/2).
$C_{23}H_{28}O_3S$ (384.54)
Calculated: C 71.84 H 7.34 S 8.34
Found: C 71.80 H 7.58 S 8.22

Example 19

[1 - (4 - Cyclohexylphenyl) - ethylsulfinyl]-acetamide.

10.0 g (34 mmol) of [1 - (4 - cyclohexylphenyl) - ethylsulfinyl]acetic acid (m.p.: 152—154°C) were dissolved in 50 ml of absolute tetrahydrofuran and 6.1 g (37 mmol) of carbonyl diimidazole were added thereto. On cessation of carbon dioxide evolution (about 20 minutes), a dry stream of ammonia was introduced until the mixture was saturated. After standing overnight, the mixture was evaporated and the residue was distributed between water and ethyl acetate. The organic layer was washed with sodium carbonate solution and with dilute hydrochloric acid, dried and evaporated. The residue was recrystallized from isopropanol.

Yield: 7.5 g (75.4% of theory),
m.p.: 199—201°C.
$C_{16}H_{23}NO_2S$ (293.44)
Calculated:
C 65.49 H 7.90 N 4.77 S 10.93
Found:
C 65.60 H 7.95 N 4.99 S 10.86

Example 20

[1 - (4 - Cyclohexylphenyl) - ethylsulfinyl]-acetic acid isopropylamide

Prepared analogously to Example 19 from [1 - (4 - cyclohexylphenyl) - ethylsulfinyl]-acetic acid (m.p.: 152—154°C) and isopropylamine using carbonyl diimidazole. Purification of the product was effected by filtration on silica gel with ethyl acetate.

Yield: 82% of theory,
m.p.: 124—126°C (from cyclohexane)
$C_{19}H_{29}NO_2S$ (335.52)
Calculated:
C 68.02 H 8.71 N 4.18 S 9.56
Found:
C 68.00 H 8.98 N 4.20 S 9.38

Example 21

[1 - (4 - Cyclohexylphenyl) - ethylsulfinyl]-acetic acid morpholide

Prepared analogously to Example 19 from [1 - (4 - cyclohexylphenyl) - ethylsulfinyl]-acetic acid (m.p.: 152—154°C) and morpholine using carbonyl diimidazole. Further purification of the product was carried out by filtration on silica gel with benzene - ethyl acetate - methanol=8/4/1.

Yield: 87% of theory,
m.p.: 112—114°C (from cyclohexane).
$C_{20}H_{29}NO_3S$ (363.53)
Calculated: C 66.08 H 8.04 S 8.82
Found: C 66.20 H 8.07 S 8.68

Example 22

[1 - (4 - Cyclohexylphenyl) - ethylsulfinyl]-acetic acid piperidide

Prepared analogously to Example 19 from [1 - (4 - cyclohexylphenyl) - ethylsulfinyl]-acetic acid (m.p.: 152—154°C) and piperidine using carbonyl diimidazole. Purification of the product was carried out by filtration on silica gel with ethyl acetate.

Yield: 67% of theory,
m.p.: 94—96°C (from cyclohexane).
$C_{21}H_{31}NO_2S$ (361.55)
Calculated: C 69.76 H 8.64 S 8.87
Found: C 69.60 H 8.60 S 8.89

Example 23

Diastereoisomeric [1 - (3 - chloro - 4 - cyclohexyl - phenyl) - ethylsulfinyl]acetic acids

Prepared analogously to Example 9 by oxidation of [1 - (3 - chloro - 4 - cyclohexyl - phenyl) - ethylthio]acetic acid in glacial acetic acid with hydrogen peroxide.

(a) Slightly soluble isomer
Yield: 47% of theory,
m.p.: 160—162°C (decomp., glacial acetic acid)
$C_{16}H_{21}ClO_3S$ (328.87)
Calculated:
C 58.44 H 6.44 Cl 10.78 S 9.75
Found:
C 58.30 H 6.26 Cl 10.88 S 9.76

Characteristic signals in the NMR spectrum ($CDCl_3$—CH_3OD):
CH_2: singlet at 3.55 ppm

b) Fairly soluble isomer
Yield: 30% of theory,
m.p.: 141—143°C (decomp.) (from benzene - cyclohexane=2/1).
$C_{16}H_{21}ClO_3S$ (328.87)
Calculated:
C 58.44 H 6.44 Cl 10.78 S 9.75
Found:
C 58.50 H 6.23 Cl 10.92 S 9.78
NMR spectrum ($CDCl_3$—CD_3OD):
CH_2: double doublet at 3.65 ppm (J=7 ppm).

Example 24

Methyl [1 - (3 - chloro - 4 - cyclohexyl - phenyl) - ethylsulfinyl]acetate

Prepared analogously to Example 11 from [1 - (3 - chloro - 4 - cyclohexyl - phenyl) - ethylsulfinyl]acetic acid (slightly soluble isomer, m.p.: 160—162°C) and methyl iodide in the presence of potassium carbonate.

Yield: 66% of theory,
m.p.: 93—95°C (from cyclohexane - petroleum ether=2/1).
$C_{17}H_{23}ClO_3S$ (342.90)
Calculated:
C 59.55 H 6.76 Cl 10.34 S 9.35
Found:
C 59.80 H 6.86 Cl 10.34 S 9.34
NMR spectrum ($CDCl_3$):
CH_2: double doublet at 3.45 ppm.

Example 25

Methyl - [1 - (3 - chloro - 4 - cyclohexyl - phenyl) - ethylsulfinyl]acetate

Prepared analogously to Example 11 from [1 - (3 - chloro - 4 - cyclohexyl - phenyl) - ethylsulfinyl]acetic acid (fairly soluble isomer, m.p.: 141—143°C) and methyl iodide in the presence of potassium carbonate. Purification of the product was carried out by column chromatography on silica gel with cyclohexane - ethyl acetate=1/1.

Yield: 34% of theory,
oil, R_f value: 0.35 on carrier B with cyclohexane - ethyl acetate=1/1.
$C_{17}H_{23}ClO_3S$ (342.90)
Calculated:
C 59.55 H 6.76 Cl 10.34 S 9.35
Found:
C 59.90 H 6.96 Cl 10.13 S 9.10
NMR spectrum ($CDCl_3$):
CH_2: singlet at 3.32 ppm.

Example 26

Ethyl [1 - (3 - chloro - 4 - cyclohexyl - phenyl) - ethylsulfinyl]acetate

Prepared analogously to Example 11 from [1 - (3 - chloro - 4 - cyclohexyl - phenyl) - ethylsulfinyl]acetic acid (m.p.: 160—162°C) and ethyl iodide in the presence of potassium carbonate.

Yield: 53.6% of theory,
m.p.: 80—82°C (from cyclohexane - petroleum ether=1/2).
$C_{18}H_{25}ClO_3S$ (356.92)
Calculated:
C 60.57 H 7.06 Cl 9.93 S 8.98
Found:
C 60.50 H 7.00 Cl 9.98 S 9.10
NMR spectrum ($CDCl_3$):
CH_2: double doublet at 3.45 ppm (J= 14 Hz).

Example 27

Ethyl [1 - (3 - chloro - 4 - cyclohexyl - phenyl) - ethylsulfinyl]acetate

Prepared analogously to Example 11 from [1 - (3 - chloro - 4 - cyclohexyl - phenyl - ethylsulfinyl]acetic acid (m.p.: 141—143°C) and ethyl iodide in the presence of potassium carbonate. Purification of the product was effected by chromatography on silica gel with cyclohexane - ethyl acetate=1/1.

Yield: 27% of theory,
m.p.: 102—104°C (cyclohexane - petroleum ether=1/2).
$C_{18}H_{25}ClO_3S$ (356.92)
Calculated:
C 60.57 H 7.06 Cl 9.93 S 8.98
Found:
C 60.80 H 7.04 Cl 10.07 S 9.02

Example 28

Diastereoisomeric [1 - (3 - chloro - 4 - cyclohexyl - phenyl) - ethylsulfinyl]-acetamides

a) Isomer slightly soluble in methanol

13.4 g (42.1 mmol) of [1 - (3 - chloro - 4 - cyclohexyl - phenyl) - ethylthio] - acetamide were oxidized in 75 ml of glacial acetic acid with 4.2 g of 36.3% hydrogen peroxide at room temperature (duration: 1 hour). The reaction product thus formed was precipitated with water, isolated, dried and dissolved in 60 ml of methanol. From the solution thus obtained 6.7 g (48.5% of theory) of the product crystallized out.

M.p.: 187—189°C (decomp.).
$C_{16}H_{22}ClNO_2S$ (327.89)
Calculated:
C 58.61 H 6.76 Cl 10.81 N 4.27
S 9.78
Found:
C 59.30 H 6.85 Cl 10.63 N 4.27
S 9.62
NMR spectrum ($CDCl_3$—CH_3OD):
CH_2: double doublet at 3.4 ppm (J= 14 Hz).

b) Isomer fairly soluble in methanol

The methanol filtrate obtained above was evaporated and the residue was recrystallized from a large excess of ethyl acetate and subsequently from toluene. Yield: 3.5 g (25.4% of theory) with m.p. 145—147°C.

$C_{16}H_{23}ClNO_2S$ (327.89)
Calculated:
C 58.61 H 6.76 Cl 10.81 N 4.27
S 9.78
Found:
C 58.90 H 6.77 Cl 10.60 N 4.23
S 10.02

Example 29

[1 - (3 - Chloro - 4 - cyclohexyl - phenyl) - ethylsulfinyl]acetic acid piperidide

Prepared analogously to Example 28 from [1 - (3 - chloro - 4 - cyclohexyl - phenyl) - ethylthio]acetic acid piperidide by oxidation with hydrogen peroxide in glacial acetic acid. Purification of the product was carried out by filtration on silica gel with toluene - ethyl acetate - methanol=8/4/1. Yield: 90% of theory.

The mixture of both diastereoisomers is an oil having R_f values of 0.6 and 0.5 (carrier A with toluene - ethyl acetate - methanol= 8/4/1).

$C_{21}H_{30}ClNO_2S$ (395.99)
Calculated:
C 63.70 H 7.64 Cl 8.95 N 3.54
S 8.10
Found:
C 64.50 H 7.79 Cl 8.11 N 3.40
S 8.34

Example 30

[1 - (3 - Chloro - 4 - cyclohexyl - phenyl) - ethylsulfinyl]acetic acid morpholide

Prepared analogously to Example 28 from [1 - (3 - chloro - 4 - cyclohexyl - phenyl) - ethylthio]acetic acid morpholide by oxidation with hydrogen peroxide in glacial acetic acid. Purification of the product was carried out by filtration on silica gel with toluene - ethyl acetate - methanol = 8/4/1. Yield: 83% of theory.

The mixture of both diastereoisomers is an oil having R_f values of 0.4 and 0.3 (carrier B with toluene - ethyl acetate - methanol = 8/4/1).

$C_{20}H_{28}ClNO_3S$ (39.96)

Calculated:
C 60.36 H 7.09 Cl 8.91 N 3.52 S 8.06

Found:
C 60.70 H 7.19 Cl 8.68 N 3.31 S 7.90

Example 31

[1 - (4 - Cyclohexylphenyl) - ethylsulfonyl]-acetic acid

5.0 g (17 mmol) of [1 - (4 - cyclohexylphenyl)-ethylsulfinyl]acetic acid (m.p.: 152—154°C) were suspended in 50 ml of glacial acetic acid and 10 ml of water and 2.7 g (17 mmol) of potassium permanganate were added thereto in small amounts at 20 to 25°C whilst stirring vigorously. The mixture obtained was stirred for a further hour and then mixed with 150 ml of water. The manganese dioxide thus formed was reduced with sodium sulfite and the reaction product was extracted with ethyl acetate. The extracts were washed with water, dried and evaporated. The residue was crystallized from cyclohexane.

Yield: 4.1 g (77% of theory).
m.p.: 104—105°C.
Calculated: C 61.91 H 7.14 S 10.33
Found: C 61.90 H 7.14 S 10.38
Characteristic IR bands (CH_2Cl_2) and 1130 and 1310 cm^{-1} (SO_2).

Example 32

Methyl [1 - (4 - cyclohexylphenyl) - ethylsulfonyl]acetate

Prepared analogously to Example 31 from methyl [1 - (4 - cyclohexylphenyl) - ethylsulfinyl]acetate (m.p.: 112—114°C) by oxidation with potassium permanganate.

Yield: 83% of theory,
m.p.: 81—83°C (from cyclohexane).
$C_{17}H_{24}O_4S$ (324.45)
Calculated: C 62.93 H 7.46 S 9.88
Found: C 62.80 H 7.40 S 9.96

Characteristic IR bands (CH_2Cl_2) at 1130 and 1310 cm^{-1} (SO_2).

Example 33

[1 - (4 - Cyclohexylphenyl) - ethylsulfonyl]-acetamide

Prepared analogously to Example 31 from [1 - (4 - cyclohexylphenyl) - ethylsulfinyl]acetamide by oxidation with potassium permanganate.

Yield: 75% of theory,
m.p.: 150—152°C (from benzene).
$C_{16}H_{23}NO_3S$ (309.44)
Calculated:
C 62.11 H 7.49 N 4.53 S 10.36
Found:
C 62.10 H 7.45 N 4.41 S 10.20

Example 34

[1 - (4 - Cyclohexylphenyl) - ethylsulfonyl]-acetic acid piperidide

Prepared analogously to Example 31 from [1 - (4 - cyclohexylphenyl) - ethylsulfinyl]-acetic acid piperidide by oxidation with potassium permanganate.

Yield: 62% of theory,
m.p.: 92—94°C (from cyclohexane - petroleum ether = 1/1).
$C_{21}H_{31}NO_3S$ (377.55)
Calculated:
C66.81 H 8.28 N 3.71 S 8.49
Found:
C 66.90 H 8.15 N 3.84 S 8.49

Example 35

[1 - (4 - Cyclohexylphenyl) - ethylsulfonyl]-acetic acid

Prepared analogously to Example 31 from [1 - (4 - cyclohexylphenyl) ethylthio]acetic acid by oxidation with twice the quantity of potassium permanganate.

Yield: 82% of theory,
m.p.: 104—105°C (from cyclohexane).

Example 36

Methyl [1 - (4 - cyclohexylphenyl) - ethylsulfonyl]acetate

Prepared analogously to Example 11 from [1 - (4 - cyclohexylphenyl) - ethylsulfonyl]-acetic acid by esterification with methyl iodide in the presence of ethyl - diisopropyl - amine.
Yield: 86% of theory,
m.p.: 82—84°C.

Example 37

[1 - (4 - Cyclohexylphenyl) - ethylsulfonyl]-acetamide

Prepared analogously to Example 19 from [1 - (4 - cyclohexylphenyl) - ethylsulfonyl]-acetic acid and ammonia using carbonyl diimidazole.

Yield: 78% of theory,
m.p.: 149—151°C.

Example I

Tablets containing 30 mg of [1 - (4 - cyclohexylphenyl) - ethylsulfinyl]acetic acid

Composition:

1 tablet contains:	
Active ingredient	30.0 mg
lactose	38.0 mg
potato starch	26.0 mg
polyvinylpyrrolidone	5.0 mg
magnesium stearate	1.0 mg
	100.0 mg

Method of preparation:

The active ingredient, mixed with the lactose and potato starch, was homogeneously moistened with a 20% ethanolic solution of the polyvinylpyrrolidone and then passed through a screen of 1.5 mm mesh size. The granulate obtained was dried at 45°C and then passed through a screen of 1.0 mm mesh size.

The granulate thus obtained was mixed with the magnesium stearate and pressed into tablets.

Weight of tablet: 100 mg
Punch: 7 mm, flat

Example II

Coated tablets containing 15 mg of [1 - (4 - cyclohexylphenyl) - ethylsulfinyl]acetic acid

Composition:

1 coated tablet core contains:	
Active ingredient	15.0 mg
lactose	14.0 mg
corn starch	8.0 mg
polyvinylpyrrolidone	2.5 mg
magnesium stearate	0.5 mg
	40.0 mg

Method of preparation:

The active ingredient, mixed with the lactose and corn starch, was homogeneously moistened with a 20% ethanolic solution of the polyvinylpyrrolidone and passed through a screen of 1.5 mm mesh size. The granulate obtained was dried at 45°C and then passed through a screen of 1.0 mm mesh size.

The granulate thus obtained was mixed with the magnesium stearate and pressed into coated tablet cores.

Weight of core: 40.0 mg
Punch: 5.0 mm, arcuate

The cores were covered according to known methods with a coating consisting essentially of sugar and talcum. The finished tablets were polished with beeswax.

Weight of coated tablet: 70.0 mg.

Example III

Ampoules conatining 10 mg of [1 - (4 - cyclohexylphenyl) - ethylsulfinyl] - acetic acid

Composition:

1 ampoule contains:	
Active ingredient	10.0 mg
polyethyleneglycol 600	100.0 mg
distilled water	ad 2.0 ml

Method of preparation:

The polyethyleneglycol and the active ingredient were dissolved, under nitrogen, in water which had been boiled, cooled under nitrogen and distilled. The solution obtained was made up to the given volume with pretreated water and then filtered under sterile conditions. The preparation was effected in diffuse light. Filling: Into brown ampoules of 2 ml capacity under nitrogen.
Sterilization: 20 minutes at 120°C.

Example IV

Drop solution containing 10 mg/ml of [1 - (4 - cyclohexylphenyl) - ethylsulfinyl]-acetic acid

Composition:

1 ml of drop solution contains:	
Active ingredient	10.0 mg
cane sugar	350.0 mg
sorbic acid	1.0 mg
cocoa essence	50.0 mg
ethanol	0.2 ml
polyethyleneglycol 600	0.1 ml
distilled water	ad 1.0 ml

Method of preparation:

The sorbic acid was dissolved in the ethanol, an equal quantity of water was added thereto and then the active ingredient was dissolved therein (solution 1). The sugar was dissolved in the remaining water (solution 2).

Solution 2, the polyethyleneglycol 600 and the cocoa essence were added, with stirring, to solution 1. The mixture was filtered through a suitable filter.

1 ml of drop solution ≙ 10 mg of active ingredient. Preparation, filling and storing of the solution was effected under nitrogen and with protection against light.

Example V

Suppositories containing 50 mg of [1 - (4 - cyclohexylphenyl) - ethylsulfinyl]acetic acid

Composition:

1 suppository contains:	
Active ingredient	50.0 mg
suppository mass (e.g. "Witepsol" [registered Trade Mark] W 45)	1,500.0 mg
	1,550.0 mg

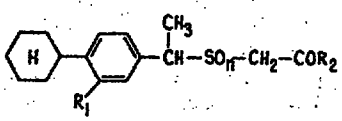
Method of preparation:

The finely pulverized active ingredient was stirred into the molten suppository mass, cooled to 40°C, by means of an immersion homogenizer. The mass obtained was poured into slightly pre-cooled moulds at 38°C.

Weight of suppository: 1.55 g.

WHAT WE CLAIM IS:—

1. Compounds of general formula I,



(I)

wherein

R_1 represents a hydrogen or halogen atom;

R_2 represent a hydroxy group, an alkoxy group containing from 1 to 6 carbon atoms, an aralkoxy group containing from 7 to 10 carbon atoms, an amino group (optionally substituted by an alkyl group containing from 1 to 3 carbon atoms), a piperidino group or a morpholino group; and

n is 0, 1 or 2;

and, where R_2 represents a hydroxy group, the salts thereof.

2. Compounds as claimed in claim 1 wherein R_1 represents a hydrogen or chlorine atom.

3. Compounds as claimed in claim 1 or claim 2 wherein R_2 represents a hydroxy, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isoamyloxy, hexyloxy, benzyloxy, amino, isopropylamino, piperidino or morpholino group.

4. [1 - (4 - Cyclohexylphenyl) - ethylsulfinyl]acetic acid and salts thereof.

5. Methyl [1 - (4 - cyclohexylphenyl) - ethylsulfinyl]acetate.

6. Methyl [1 - (3 - chloro - 4 - cyclohexyl - phenyl) - ethylsulfinyl] - acetate.

7. Ethyl [1 - (3 - chloro - 4 - cyclohexyl - phenyl) - ethylsulfinyl] - acetate.

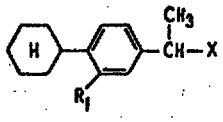
8. [1 - (3 - Chloro - 4 - cyclohexyl - phenyl) - ethylsulfinyl] - acetic acid piperidide and salts thereof.

9. Compounds of general formula I as defined in claim 1, wherein R_2 represents a hydroxy group, in the form of a physiologically compatible salt.

10. Compounds as claimed in any of the preceding claims in the form of an optically active isomer.

11. Compounds as claimed in claim 1, other than those claimed in any of claims 4 to 8, as herein specifically disclosed in any one of Examples 1 to 37.

12. A process for the preparation of compounds of general formula I as defined in claim 1 wherein n is 0 which comprises reacting a compound of formula II,



(II)

(wherein R_1 is as defined in claim 1 and X represents a halogen atom or a hydroxy group) with a compound of formula III,

$$HS—CH_2—COR_2 \qquad (III)$$

wherein R_2 is as defined in claim 1).

13. A process as claimed in claim 12 wherein the reaction is effected in the presence of dimethylsulfoxide as solvent.

14. A process as claimed in claim 12 or claim 13 wherein the reaction is effected at temperatures of from 0 to 100°C.

15. A process as claimed in claim 14 wherein the reaction is effected at temperatures of from 5 to 30°C.

16. A process as claimed in any of claims 12 to 15 wherein the reaction is effected in the presence of a base.

17. A process as claimed in claim 16 wherein the base is potassium carbonate, triethylamine or pyridine.

18. A process as claimed in any of claims 12 to 15, for the preparation of compounds of general formula I in which X represents a hydroxy group, wherein the reaction is effected in the presence of an acid.

19. A process as claimed in claim 18 wherein the acid is hydrochloric or sulfuric acid.

20. A process for the preparation of compounds of general formula I as defined in claims 1 wherein n is 1 or 2 which comprises oxidising a compound of formula I as defined in claim 1 (wherein n is less than the value of n in the desired compound of formula I) whereby the desired compound of formula I is obtained.

21. A process as claimed in claim 20 wherein the oxidation is effected in the presence of a solvent.

22. A process as claimed in claim 21 wherein the solvent is water, aqueous pyridine, acetone, glacial acetic acid, dilute sulfuric acid or trifluoroacetic acid.

23. A process as claimed in any of claims 20 to 22 wherein the oxidation is effected at temperatures of from −80 to 100°C.

24. A process as claimed in any of claims 20 to 23 for the preparation of compounds of general formula I wherein n is 1, which comprises oxidising a compound of formula I wherein n is 0.

25. A process as claimed in claim 24 wherein oxidation is effected by reaction of the compound of formula I wherein n is 0 with a substantially equimolar quantity of an oxidising agent.

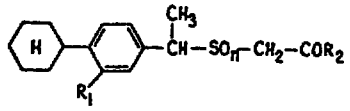
26. A process as claimed in claim 24 or

Method of preparation:

The finely pulverized active ingredient was stirred into the molten suppository mass, cooled to 40°C, by means of an immersion homogenizer. The mass obtained was poured into slightly pre-cooled moulds at 38°C. Weight of suppository: 1.55 g.

WHAT WE CLAIM IS:—

1. Compounds of general formula I,



(I)

wherein

R_1 represents a hydrogen or halogen atom;

R_2 represent a hydroxy group, an alkoxy group containing from 1 to 6 carbon atoms, an aralkoxy group containing from 7 to 10 carbon atoms, an amino group (optionally substituted by an alkyl group containing from 1 to 3 carbon atoms), a piperidino group or a morpholino group; and

n is 0, 1 or 2;

and, where R_2 represents a hydroxy group, the salts thereof.

2. Compounds as claimed in claim 1 wherein R_1 represents a hydrogen or chlorine atom.

3. Compounds as claimed in claim 1 or claim 2 wherein R_2 represents a hydroxy, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isoamyloxy, hexyloxy, benzyloxy, amino, isopropylamino, piperidino or morpholino group.

4. [1 - (4 - Cyclohexylphenyl) - ethylsulfinyl]acetic acid and salts thereof.

5. Methyl [1 - (4 - cyclohexylphenyl) - ethylsulfinyl]acetate.

6. Methyl [1 - (3 - chloro - 4 - cyclohexyl - phenyl) - ethylsulfinyl] - acetate.

7. Ethyl [1 - (3 - chloro - 4 - cyclohexyl - phenyl) - ethylsulfinyl] - acetate.

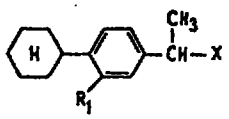
8. [1 - (3 - Chloro - 4 - cyclohexyl - phenyl) - ethylsulfinyl] - acetic acid piperidide and salts thereof.

9. Compounds of general formula I as defined in claim 1, wherein R_2 represents a hydroxy group, in the form of a physiologically compatible salt.

10. Compounds as claimed in any of the preceding claims in the form of an optically active isomer.

11. Compounds as claimed in claim 1, other than those claimed in any of claims 4 to 8, as herein specifically disclosed in any one of Examples 1 to 37.

12. A process for the preparation of compounds of general formula I as defined in claim 1 wherein n is 0 which comprises reacting a compound of formula II,



(II)

(wherein R_1 is as defined in claim 1 and X represents a halogen atom or a hydroxy group) with a compound of formula III,

$$HS—CH_2—COR_2 \qquad (III)$$

wherein R_2 is as defined in claim 1).

13. A process as claimed in claim 12 wherein the reaction is effected in the presence of dimethylsulfoxide as solvent.

14. A process as claimed in claim 12 or claim 13 wherein the reaction is effected at temperatures of from 0 to 100°C.

15. A process as claimed in claim 14 wherein the reaction is effected at temperatures of from 5 to 30°C.

16. A process as claimed in any of claims 12 to 15 wherein the reaction is effected in the presence of a base.

17. A process as claimed in claim 16 wherein the base is potassium carbonate, triethylamine or pyridine.

18. A process as claimed in any of claims 12 to 15, for the preparation of compounds of general formula I in which X represents a hydroxy group, wherein the reaction is effected in the presence of an acid.

19. A process as claimed in claim 18 wherein the acid is hydrochloric or sulfuric acid.

20. A process for the preparation of compounds of general formula I as defined in claims 1 wherein n is 1 or 2 which comprises oxidising a compound of formula I as defined in claim 1 (wherein n is less than the value of n in the desired compound of formula I) whereby the desired compound of formula I is obtained.

21. A process as claimed in claim 20 wherein the oxidation is effected in the presence of a solvent.

22. A process as claimed in claim 21 wherein the solvent is water, aqueous pyridine, acetone, glacial acetic acid, dilute sulfuric acid or trifluoroacetic acid.

23. A process as claimed in any of claims 20 to 22 wherein the oxidation is effected at temperatures of from −80 to 100°C.

24. A process as claimed in any of claims 20 to 23 for the preparation of compounds of general formula I wherein n is 1, which comprises oxidising a compound of formula I wherein n is 0.

25. A process as claimed in claim 24 wherein oxidation is effected by reaction of the compound of formula I wherein n is 0 with a substantially equimolar quantity of an oxidising agent.

26. A process as claimed in claim 24 or

claim 25 wherein oxidation is effected by means of hydrogen peroxide.

27. A process as claimed in claim 26 wherein the oxidation is effected in the presence of glacial acetic acid.

28. A process as claimed in claim 27 wherein the oxidation is effected at temperatures of from 0 to 20°C.

29. A process as claimed in claim 26 wherein the oxidation is effected in the presence of acetone.

30. A process as claimed in claim 26 or claim 29 wherein the oxidation is effected at temperatures of from 0 to 60°C.

31. A process as claimed in claim 24 or claim 25 wherein oxidation is effected by means of a peracid.

32. A process as claimed in claim 31 wherein the peracid is performic acid.

33. A process as claimed in claim 31 or claim 32 wherein the oxidation is effected in the presence of glacial acetic or trifluoroacetic acid.

34. A process as claimed in any of claims 31 to 33 wherein the oxidation is effected at temperatures of from 0 to 50°C.

35. A process as claimed in claim 24 or claim 25 wherein oxidation is effected by means of sodium metaperiodate.

36. A process as claimed in claim 35 wherein the oxidation is effected in the presence of aqueous methanol or ethanol.

37. A process as claimed in claim 35 or claim 36 wherein the oxidation is effected at temperatures of from 15 to 25°C.

38. A process as claimed in claim 24 or claim 25 wherein oxidation is effected by means of tert. - butyl hypochlorite.

39. A process as claimed in claim 38 wherein the oxidation is effected in the presence of methanol.

40. A process as claimed in claim 38 or 39 wherein the oxidation is effected at temperatures of from −80 to −30°C.

41. A process as claimed in claim 24 or claim 25 wherein oxidation is effected by means of iodobenzene dichloride.

42. A process as claimed in claim 41 wherein the oxidation is effected in aqueous pyridine.

43. A process as claimed in claim 41 or claim 42 wherein the oxidation is effected at temperatures of from 0 to 5°C.

44. A process as claimed in claim 24 or claim 25 wherein oxidation is effected by means of nitric acid.

45. A process as claimed in claim 44 wherein the oxidation is effected in the presence of glacial acetic acid.

46. A process as claimed in claim 24 or claim 25 wherein oxidation is effected by means of chromic acid.

47. A process as claimed in claim 46 wherein the oxidation is effected in the presence of glacial acetic acid or acetone.

48. A process as claimed in any of claims 44 to 47 wherein the oxidation is effected at temperatures of from 0 to 20°C.

49. A process as claimed in claim 20 for the preparation of compounds of general formula I wherein n is 2 which comprises oxidising a compound of formula I wherein n is 1.

50. A process as claimed in claim 49 wherein oxidation is effected by reaction of the compound of formula I wherein n is 1 with a substantially equimolar quantity of an oxidising agent.

51. A process as claimed in claim 20 for the preparation of compounds of general formula I wherein n is 2 which comprises oxidising a compound of formula I wherein n is 0.

52. A process as claimed in claim 51 wherein oxidation is effected by reaction of the compound of formula I wherein n is 0 with an oxidising agent in a molar ratio of substantially 1:2.

53. A process as claimed in any of claims 49 to 52 wherein oxidation is effected by means of hydrogen peroxide.

54. A process as claimed in claim 53 wherein the oxidation is effected in the presence of glacial acetic acid.

55. A process as claimed in claim 54 wherein the oxidation is effected at temperatures of from 20 to 100°C.

56. A process as claimed in claim 53 wherein the oxidation is effected in the presence of acetone.

57. A process as claimed in claim 56 wherein the oxidation is effected at temperatures of from 0 to 60°C.

58. A process as claimed in any of claims 49 to 52 wherein oxidation is effected by means of a peracid.

59. A process as claimed in claim 58 wherein the peracid is performic or *m* - chloroperbenzoic acid.

60. A process as claimed in claim 58 or claim 59 wherein the oxidation is effected in the presence of glacial acetic acid, trifluoroacetic acid or chloroform.

61. A process as claimed in any of claims 58 to 60 wherein the oxidation is effected at temperatures of from 0 to 50°C.

62. A process as claimed in any of claims 49 to 52 wherein oxidation is effected by means of nitric acid.

63. A process as claimed in claim 62 wherein the oxidation is effected in the presence of glacial acetic acid.

64. A process as claimed in any of claims 49 to 52 wherein oxidation is effected by means of chromic acid or potassium permanganate.

65. A process as claimed in claim 64 wherein the oxidation is effected in the presence of glacial acetic acid, acetone or aqueous sulfuric acid.

66. A process as claimed in any of claims 62 to 65 wherein the oxidation is effected at temperatures of from 0 to 20°C.

67. A process for the preparation of compounds of general formula I as defined in claim 1 wherein R_2 is other than a hydroxy group which comprises reacting a compound of formula I as defined in claim 1 (wherein R_2 represents a hydroxy group) or an acid halide or anhydride thereof with a compound of formula IV,

$$R_2'—Y \qquad (IV)$$

(wherein R_2' represents an alkyl group containing from 1 to 6 carbon atoms, an aralkyl group containing from 7 to 10 carbon atoms, an amino group (optionally substituted by an alkyl group containing from 1 to 3 carbon atoms), a piperidino or morpholino group and Y represents a hydroxy group, a chlorine, bromine or iodine atom or a sulfate or phosphate group or may, when R_2' represents an amino group (optionally substituted by an alkyl group containing from 1 to 3 carbon atoms), a piperidino or morpholino group, represent a hydrogen atom.

68. A process as claimed in claim 67 wherein the reaction is effected in the presence of ether, chloroform, benzene, tetrahydrofuran, dioxan, dimethylformamide, dimethylsulfoxide, hexamethylphosphoric acid triamide or an excess of the compound of formula IV as solvent.

69. A process as claimed in claim 67 or claim 68 wherein the reaction is effected in the presence of an acid activating agent, a dehydrating agent and/or a base.

70. A process as claimed in any of claims 67 to 69 wherein the reaction is effected at temperatures of from −20 to 150°C.

71. A process as claimed in any of claims 67 to 70 wherein, in the compound of formula IV, Y represents a hydroxy group.

72. A process as claimed in claim 71 wherein the reaction is effected in the presence of an acid.

73. A process as claimed in claim 72 wherein the acid is sulfuric, *p* - toluenesulfonic or hydrochloric acid.

74. A process as claimed in any of claims 71 to 73 wherein the reaction is effected in the presence of phosphorus oxychloride, thionyl chloride or chlorosulfonic acid as an acid activating agent.

75. A process as claimed in any of claims 71 to 74 wherein the reaction is effected in the presence of cyclohexylcarbodiimide, carbonyl diimidazole or 2,2 - dimethoxypropane as a dehydrating agent.

76. A process as claimed in any of claims 71 to 75 wherein the reaction is effected in the presence of a corresponding chloroformic acid ester.

77. A process as claimed in any of claims 71 to 76 wherein the reaction is effected in the presence of potassium carbonate or triethylamine as a base.

78. A process as claimed in any of claims 71 to 77 wherein the reaction is effected at temperatures of from 20 to 100°C.

79. A process as claimed in any of claims 67 to 70 wherein, in the compound of formula IV, Y represents a sulfate or phosphate group or a chlorine, bromine or iodine atom.

80. A process as claimed in claim 79 wherein the reaction is effected in the presence of a dipolar aprotic solvent.

81. A process as claimed in claim 79 or claim 80 wherein the reaction is effected in the presence of potassium carbonate, calcium hydroxide or sodium hydroxide as a base.

82. A process as claimed in any of claims 79 to 81 wherein the reaction is effected at temperatures of from 20 to 80°C.

83. A process as claimed in claim 79 wherein the reaction is effected as a phase transfer-catalysed two-phase reaction.

84. A process as claimed in claim 83 wherein the reaction is effected in the presence of chloroform and water.

85. A process as claimed in claim 83 or claim 84 wherein the reaction is effected in the presence of a quaternary ammonium salt.

86. A process as claimed in claim 85 wherein the quaternary ammonium salt is tetrabutylammonium iodide.

87. A process as claimed in any of claims 67 to 70 wherein, in the compound of formula IV, Y represents a hydrogen atom.

88. A process as claimed in claim 87 wherein the reaction is effected in the presence of cyclohexylcarbodiimide or carbonyl diimidazole as a dehydrating agent.

89. A process as claimed in claim 87 or claim 88 wherein the reaction is effected in the presence of dioxan or tetrahydrofuran as solvent.

90. A process as claimed in any of claims 87 to 89 wherein the reaction is effected at temperatures of from 10 to 50°C.

91. A process for the preparation of compounds of general formula I as defined in claim 1 wherein R_2 represents a hydroxy group which comprises hydrolysing a compound of formula I as defined in claim 1 (wherein R_2 is other than a hydroxy group).

92. A process for the preparation of physiologically compatible salts of compounds of general formula I as defined in claim 1 wherein R_2 represents a hydroxy group which comprises reacting a compound of formula I as defined in claim 1 (wherein R_2 represents a hydroxy group) with an appropriate base.

93. A process as claimed in claim 92 wherein the base is sodium hydroxide, potassium hydroxide or cyclohexylamine.

94. A process for the preparation of compounds of general formula I as defined in claim 1 or, where R_2 represents a hydroxy group, a physiologically compatible salt there-

of in the form of an optically active isomer which comprises separating an isomeric mixture thereof.

95. A process for the preparation of compounds of general formula I as defined in claim 1 and, where R_2 represents a hydroxy group, the physiologically compatible salts thereof substantially as herein described.

96. A process for the preparation of compounds of general formula I as defined in claim 1 and, where R_2 represents a hydroxy group, the physiologically compatible salts thereof substantially as herein described in any one of Examples 1 to 37.

97. Compounds of general formula I as defined in claim 1 and, where R_2 represents a hydroxy group, the physiologically compatible salts thereof whenever prepared by a process as claimed in any of claims 12 to 96.

98. Pharmaceutical compositions comprising, as active ingredient, at least one compound of formula I or, where R_2 represents a hydroxy group, a physiologically compatible salt thereof in association with a pharmaceutical carrier or excipient.

99. Compositions as claimed in claim 98 in a form suitable for oral, rectal or parenteral administration.

100. Compositions as claimed in claim 98 or claim 99 in the form of tablets, coated tablets, solutions, suspensions, ampoules or suppositories.

101. Compositions as claimed in any of claims 98 to 100 in the form of dosage units.

102. Compositions as claimed in claim 101 wherein each dosage unit contains from 10 to 50 mg of active ingredient.

103. Compositions as claimed in any of claims 98 to 102, wherein the active ingredient is a compound as defined in any of claims 4 to 8.

104. Pharmaceutical compositions as claimed in claim 98 substantially as herein described.

105. Pharmaceutical compositions substantially as herein described in any one of Examples I to V.

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