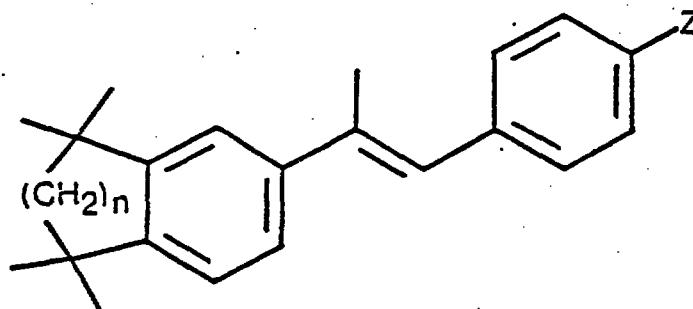


Specification

The invention is concerned with novel tetrahydronaphthalene and indane compounds of the formula



wherein n signifies 1 or 2; Z signifies mercapto or a group $-S(O)_mR$, m signifies 0, 1 or 2; R signifies lower-alkyl, lower-alkenyl, lower-alkoxy-lower-alkyl, lower-alkanoyl-lower-alkyl, hydroxy-lower-alkyl, halo-lower-alkyl, lower-carbalkoxy-lower-alkyl or, when m signifies 1 or 2, also lower-alkoxy, hydroxy, mono-lower-alkylamino or di-lower-alkylamino,

10

15

and pharmaceutically compatible salts of sulphonic acids and sulphinic acids of formula I.

Furthermore, the invention is concerned with a process for the manufacture of the compounds of formula I, intermediates in this process and pharmaceutical preparations based on compounds of formula I.

The term "lower" used herein denotes groups which preferably contain 1-4 C-atoms. Alkyl groups can be straight-chain or branched-chain. Preferred lower-alkyl groups are methyl, ethyl and isopropyl. Examples of lower-alkenyl groups are vinyl, allyl and methallyl. Examples of lower-alkanoyl groups are acetyl, propionyl and butyryl. The term "halogen" embraces fluorine, chlorine, bromine and iodine, of which chlorine is preferred. Examples of lower-carbalkoxy-lower-alkyl groups are carbomethoxy- and carboethoxy-methyl and -ethyl. Examples of lower-alkoxy groups are methoxy and ethoxy. Examples of alkylamino groups are methylamino, ethylamino, isopropylamino, dimethylamino and diethylamino. The pharmaceutically compatible salts referred to herein can be, for example, alkali metal salts and alkaline earth metal salts as well as ammonium salts.

Of the compounds of formula I there are preferred those in which R signifies lower-alkyl, lower-alkenyl, hydroxy-lower-alkyl, halo-lower-alkyl, lower-carbalkoxy-lower-alkyl or, when m signifies 1 or 2, also lower-alkoxy, hydroxy, mono-lower-alkylamino or di-lower-alkylamino.

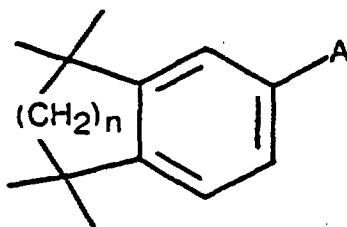
Further preferred compounds of formula I are those in which n signifies 2. Furthermore, there are preferred compounds of formula I in which m signifies 2 as well as those in which R signifies lower-alkyl, hydroxy, lower-alkoxy, lower-alkylamino, hydroxy-lower-alkyl or lower-carbalkoxy-lower-alkyl.

The following compounds are of particular interest:

Ethyl p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]benzenesulphonate;
ethyl p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]phenylsulphone;
ethyl p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]phenylsulphoxide;
ethyl p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-propenyl]phenylsulphide;
isopropyl p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]phenylsulphone.

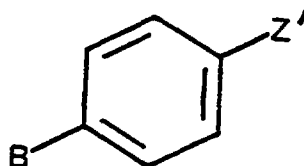
The compounds of formula I, can be manufactured in accordance with the invention by

(a) reacting a compound of the formula



II

5 with a compound of the formula



III

wherein n has the significance given above, Z' signifies $-\text{SO}_3^- \text{M}^+$, $-\text{SO}_2^- \text{M}^+$, lower-alkylthio, lower-alkylsulphanyl or lower-alkylsulphonyl and either A signifies a triarylphosphoniummethyl group of the formula $\text{H}_3\text{C}-\text{CH}-\text{P}[\text{Q}]_3^+ \text{Y}^-$ and B signifies formyl; or A signifies acetyl and B

(24)

signifies a dialkoxyphosphonylmethyl

group of the formula $-\text{CH}_2-\overset{\text{O}}{\underset{\text{||}}{\text{P}}}[\text{T}]_2$;

whereby Q denotes aryl, T denotes

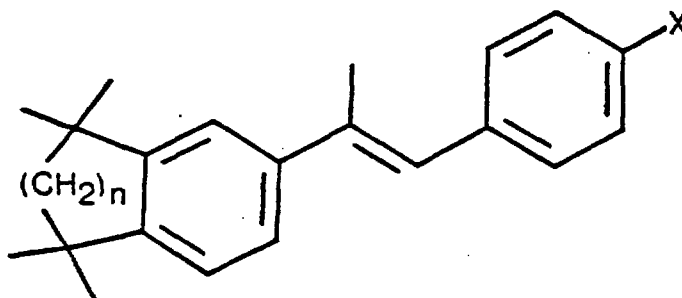
lower-alkoxy, Y^- denotes the anion

of an organic or inorganic acid and

M^+ denotes a cation,

or

(b) reacting a compound of the formula



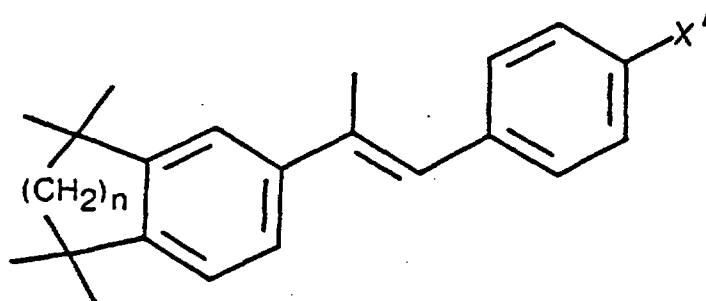
IV

10 wherein n has the above significance

and X signifies halogen,

with sulphur dioxide in the presence of a strong base, or

(c) subjecting a compound of the formula



V

wherein n has the above significance
and X' signifies di-lower-alkyl-
carbamoylthio,

5 to treatment with a base or to reduction with a complex
metal hydride, and, if desired, functionally modifying
the group denoted by Z in a compound of formula I obtained
according to (a), (b) or (c).

The reaction in accordance with process variant
10 (a) can be carried out in a manner known per se for the
Wittig and Horner reaction or under the conditions known
per se for these reactions.

The reaction of a compound of formula II in which
A represents a triarylphosphoniummethyl group with a
15 compound of formula III (Wittig reaction) is carried out
in the presence of an acid-binding agent, for example in

the presence of a strong base such as butyl lithium, sodium hydride or the sodium salt of dimethyl sulphoxide, but especially in the presence of an ethylene oxide optionally substituted by lower alkyl such as 1,2-butylene oxide, if
5 desired in a solvent (e.g. an ether such as diethyl ether or tetrahydrofuran or an aromatic hydrocarbon such as benzene) at a temperature between room temperature and the boiling point of the reaction mixture.

The aryl groups denoted by Q in the aforementioned
10 triarylphosphonium groups include all generally known aryl groups, but especially mononuclear aryl groups such as phenyl, lower-alkyl-substituted phenyl or lower-alkoxy-substituted phenyl (e.g. tolyl, xylyl, mesityl or p-methoxyphenyl).

15 Of the inorganic acid anions Y the chloride ion, the bromide ion and the hydrosulphate ion are preferred and, of the organic acid anions, the tosyloxy ion is preferred.

The alkoxy groups denoted by T in the dialkoxy-phosphonylmethyl group of the formula $-\text{CH}_2-\text{P}(\text{T})_2$ are
20 preferably lower alkoxy groups containing 1-6 carbon atoms (e.g. methoxy or ethoxy).

The reaction of a compound of formula II in which A signifies acetyl with a compound of formula III in which

B signifies a dialkoxyphosphonylmethyl group (Horner reaction) is carried out with the aid of a base and preferably in the presence of an inert organic solvent, for example with the aid of sodium hydride in benzene, 5 toluene, dimethylformamide, tetrahydrofuran, dioxan or 1,2-dimethoxyalkane, or with the aid of a sodium alcoholate in an alkanol, for example sodium methylate in methanol, at a temperature between 0° and the boiling point of the reaction mixture.

10 In accordance with process variant (a) there are obtained compounds of formula I in which Z signifies one of the groups denoted by Z'.

In accordance with process variant (b), a compound of formula IV in which X signifies halogen, preferably 15 bromine, is treated with a strong base such as butyl lithium and reacted with sulphur dioxide. The reaction can be carried out in an inert organic solvent, for example an ether such as diethyl ether or a hydrocarbon such as hexane or mixtures thereof, conveniently at a temperature 20 below room temperature (e.g. at about 0°C). Process variant (b) yields salts of sulphinic acids of formula I, i.e. compounds of formula I in which Z represents a group $-\text{SO}_2^-\text{M}^+$.

In accordance with process variant (c), a compound of formula V is treated with a base or is reduced with a complex metal hydride. Suitable bases are, for example, alkali metal hydroxides such as potassium hydroxide. The treatment is conveniently carried out in an inert solvent using an alcoholic alkali hydroxide solution at a temperature up to the reflux temperature of the mixture and yields compounds of formula I in which Z signifies mercapto. Suitable complex metal hydrides are those which are known for the reduction of an ester to the alcohol such as especially lithium aluminium hydride. The reduction can be carried out under the conditions which are known for such ester reductions, for example in a solvent such as diethyl ether or tetrahydrofuran at a temperature of about 0° to the reflux temperature of the mixture.

As functional modifications of the group denoted by Z in a compound of formula I there come into consideration the conversion of a sulphonic acid salt or a sulphinic acid salt into the corresponding free acid or an ester; the conversion of a sulphonic acid or sulphinic acid into a mono-lower-alkylamide or di-lower-alkylamide; the conversion of a sulphinic acid salt into a sulphone; the oxidation of a sulphide to the sulphoxide and the oxidation of a sulphoxide to the sulphone; the conversion of a hydroxy-lower-alkyl group into a halo-lower-alkyl group and the transformation of the latter group into a lower-

-alkenyl group; and the alkylation of a mercaptan to the alkyl sulphide or a Michael addition with a suitable Michael acceptor such as methyl acrylate or methyl vinyl ketone.

- 5 A sulphonate or sulphinate, i.e. a compound of formula I in which Z signifies $-\text{SO}_3^-\text{M}^+$ or $-\text{SO}_2^-\text{M}^+$, can be converted into the corresponding sulphonic acid or sulphinic acid, i.e. a compound of formula I in which Z signifies SO_3H or SO_2H , by treatment with an acid (e.g.
- 10 a mineral acid such as hydrochloric acid). The conversion of a sulphonic acid or a sulphinic acid into an amide, i.e. a compound of formula I in which Z signifies mono- or di-lower-alkylamino-sulphonyl or -sulphinyl, can be carried out in a manner known per se: for example, by converting
- 15 the acid into an acid halide (e.g. using thionyl chloride) and reacting the acid halide with a mono-lower-alkylamide or di-lower-alkylamine. Esters, i.e. compounds of formula I in which Z signifies lower-alkoxy-sulphonyl or -sulphinyl, can be obtained from sulphonates or sulphinates, i.e.
- 20 compounds of formula I in which Z signifies $-\text{SO}_3^-\text{M}^+$ or $-\text{SO}_2^-\text{M}^+$ by reaction with an alkylating agent such as triethoxonium tetrafluoroborate or a dialkyl sulphate, (e.g. dimethyl sulphate or diethyl sulphate). The oxidation
- 25 of a sulphide, i.e. a compound of formula I in which Z signifies lower-alkylthio, to give the corresponding sulphoxide (Z = lower-alkylsulphinyl) as well as the

oxidation of a sulphoxide to the corresponding sulphone
(Z = lower-alkylsulphonyl) can be carried out by treat-
ment with oxidizing agents such as peracids (e.g. m-
-chloroperbenzoic acid). A sulphide can also be oxidized
5 to the sulphoxide with periodates (e.g. sodium periodate).

A lower-alkyl thioether or a lower-alkyl-sulphoxide
or -sulphone [Z = $-S(O)_m R$, R = lower-alkyl] can be converted
into a corresponding lower-carbalkoxy-lower-alkyl derivative,
i.e. a compound of formula I in which Z signifies $-S(O)_m R$
10 and R signifies lower-carbalkoxy-lower-alkyl, by, for
example, treating the lower-alkyl compound (e.g. a lower-
-alkyl-sulphone) with a strong base (e.g. butyl lithium)
and reacting the metal-organic compound with a lower-
-carbalkoxy-lower-alkyl halide (e.g. ethyl chloroacetate) or
15 with an alkanoylating agent such as an alkanecarboxylic
acid ester or an alkanoyl halide.

A hydroxy-lower-alkyl thioether, -sulphoxide or
-sulphone can be converted by replacing the hydroxy group
by a halogen atom (e.g. using a halogenating agent such as
20 thionyl chloride) into the corresponding halo-lower-alkyl
derivative [Z = $-S(O)_m R$, R = halo-lower-alkyl] from which
there can be obtained by treatment with a base (e.g. an
amine such as triethylamine) a lower-alkenyl thioether or
a lower-alkenylsulphoxide or -sulphone [Z = $-S(O)_m R$, R =
25 lower-alkenyl].

The starting materials of formulae II, III, IV and V can be prepared, insofar as their preparation is not known or described hereinafter, in analogy to known processes or processes described hereinafter.

5 The compounds of formula I and their pharmaceutically compatible salts are pharmacodynamically valuable compounds. They can be used for the topical and systemic therapy of benign and malignant neoplasms and of premalignant lesions as well as for the systemic and topical prophylaxis of
10 these conditions.

They are also suitable for the topical and systemic therapy of acne, psoriasis and other dermatoses associated with an intensified or pathologically altered conification as well as of inflammatory and allergic dermatological
15 conditions. The compounds of formula I and their pharmaceutically compatible salts can also be used for the control of disorders of the mucous membrane associated with inflammatory or degenerative or metaplastic changes.

The compounds of formula I, which belong to the
20 class of retinoids, are distinguished vis-à-vis known retinoids in that, for example, in experimental animals they bring about a smaller weight loss which occurs frequently as a side-effect (A-hypervitaminosis) with the administration of retinoids.

The tumour-inhibiting activity of the present compounds is significant. In the papilloma test in mice [Europ. J. Cancer 10, 732 (1974)] a regression of the tumours induced with dimethylbenzanthracene and croton oil is observed. For example, in the case of intraperitoneal administration of ethyl p-[-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]phenylsulphone the diameters of the papillomae decrease in the course of 2 weeks by 56% at a dosage of 12.5 mg/kg/week, by 36% at a dosage of 6.25 mg/kg/week and by 12% at a dosage of 3 mg/kg/week.

For the treatment of these illnesses the compounds provided by the invention can be administered orally, conveniently in a dosage in the case of adults of about 5-200 mg per day, preferably 10-50 mg/day. A possible over-dosage can show itself in the form of a vitamin-A hypervitaminosis and is readily recognized by its symptoms (skin scaling, hair loss).

The dosage can be administered as a single dosage or in several divided dosages.

The compounds of formula I and their pharmaceutically compatible salts can accordingly be used as medicaments, for example in the form of pharmaceutical preparations.

The pharmaceutical preparations for systemic use can be manufactured, for example, by adding a compound of formula I or a pharmaceutically compatible salt thereof as the active ingredient to non-toxic, inert, solid
5 or liquid carriers which are usual in such preparations.

The pharmaceutical preparations can be administered enterally, parenterally or topically. For enteral administration there are suitable, for example, pharmaceutical preparations in the form of tablets, capsules,
10 dragées, syrups, suspensions, solutions and suppositories. For parenteral administration there are suitable pharmaceutical preparations in the form of infusion or injection solutions.

The dosages in which the present compounds are
15 administered can vary depending on the mode of administration and route of administration as well as according to the requirements of the patients.

The compounds provided by the present invention can be administered in one or more dosages. A preferred form
20 of administration comprises capsules containing about 5 mg, 20 mg or 50 mg of active substance.

The pharmaceutical preparations can contain inert as well as pharmacodynamically active additives. Tablets or granulates, for example, can contain a series of binding agents, filling materials, carrier materials or diluents.

5 Liquid preparations can take the form, for example, of a sterile solution which is miscible with water. Capsules can contain, in addition to the active substance, a filling material or thickening agent. Furthermore, flavour-
-improving additives, substances usually used as preserving,
10 stabilizing, moisture-retaining and emulsifying agents as well as salts for varying the osmotic pressure, buffers and other additives can also be present.

The previously mentioned carrier substances and diluents can be organic or inorganic in nature; for
15 example water, gelatine, lactose, starch, magnesium stearate, talc, gum arabic, polyalkyleneglycols and the like. A prerequisite is that all adjuvants used in the manufacture of the pharmaceutical preparations are non-toxic.

For topical administration, the pharmaceutical
20 preparations are conveniently provided in the form of ointments, tinctures, creams, solutions, lotions, sprays, suspensions and the like. Ointments, creams and solutions are preferred. These pharmaceutical preparations for topical administration can be manufactured by mixing the
25 compounds provided by the present invention as the active

ingredient with non-toxic, inert, solid or liquid carriers which are usual in such preparations and which are suitable for topical administration.

For topical administration there are conveniently
5 used about 0.05% to about 5%, preferably 0.1% to 1%,
solutions, ointments or creams.

If necessary, an anti-oxidant (e.g. tocopherol,
N-methyl- γ -tocopheramine, butylated hydroxyanisole or
butylated hydroxytoluene) can be included within the
10 pharmaceutical preparations.

The following Examples illustrate the invention.

Example 1

4.05 g of sodium hydride (50% suspension in mineral oil) are washed with absolute pentane, dried in
5 a water-jet vacuum and suspended in 100 ml of dimethyl-
formamide. At 0°C there is added dropwise thereto a
suspension of 43 g of [1-(5,6,7,8-tetrahydro-5,5,8,8-
-tetramethyl-2-naphthyl)ethyl]-triphenylphosphonium bromide
and the mixture is stirred at 0°C for 1 hour. At the same
temperature there is added dropwise to the thus-obtained
10 deep red solution a suspension of 16 g of the sodium salt
of p-formyl-benzenesulphonic acid in 200 ml of dimethyl-
formamide. After stirring at room temperature for 3 hours,
the brown-red solution is poured on to ice and evaporated
to dryness in a water-jet vacuum. The crystalline, grey
15 residue is suspended in ethyl acetate, filtered off under
suction and washed several times with ethyl acetate. Two-
fold recrystallization of the residue from boiling water
gives 10 g of sodium p-[2-(5,6,7,8-tetrahydro-5,5,8,8-
-tetramethyl-2-naphthyl)propenyl]benzenesulphonate with
20 a decomposition point above 300°C.

Example 2

2.0 g of the sodium sulphonate obtained according to
Example 1 are suspended in 70 ml of half-concentrated

hydrochloric acid, warmed for a short time and cooled in an ice-bath. The precipitate is filtered off under suction, washed with half-concentrated hydrochloric acid and water and dried at 50°C in a high vacuum. There
5 are obtained 1.9 g of p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]benzenesulphonic acid, melting point 103-110°C (decomposition).

Example 3

4.8 g of the sodium sulphonate obtained according
10 to Example 1 are suspended in 50 ml of dimethylformamide and treated with 2.0 g of thionyl chloride. After stirring at room temperature for 0.5 hour, 15 ml of ethylamine are added to the yellow suspension and the mixture is stirred at room temperature for a further 1
15 hour. The mixture is poured on to ice and extracted with ethyl acetate. The organic phase is washed with saturated sodium chloride solution, dried over sodium sulphate and evaporated. There is obtained a brown oil which is filtered with a mixture of hexane and ether (1:1)
20 over a short column containing silica gel and subsequently recrystallized from hexane/ether. There are obtained 1.6 g of N-ethyl-p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]benzenesulphonamide (colourless crystals), melting point 137-138°C.

Example 4

1.5 g of the sodium sulphonate obtained according to Example 1 are suspended in 120 ml of methylene chloride and treated with a solution of 760 mg of triethyloxonium tetrafluoroborate in 15 ml of methylene chloride. The mixture is stirred at room temperature for 45 minutes, the precipitate is filtered off under suction, washed with ether and the filtrate is evaporated. After recrystallization from isopropyl ether, there are obtained 1.3 g of ethyl p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-propenyl]benzenesulphonate in the form of lustrous platelets, melting point 155-157°C.

Example 5

13.0 g of 6-(p-bromo- α -methylstyryl)-1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene are dissolved in 300 ml of absolute ether. While cooling with ice there are added dropwise thereto 20 ml of a 2N solution of butyl lithium in hexane and the mixture is stirred at 0°C for a further 1.5 hours. Thereafter, a strong sulphur dioxide stream is conducted for 30 minutes into the mixture which is subsequently poured into a mixture of water and saturated sodium carbonate solution. The thus-obtained aqueous suspension is extracted twice with ether, the aqueous solution is filtered and the colourless

precipitate is dried at 80°C in a high vacuum. After recrystallization from boiling water, there are obtained 7.1 g of sodium p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]benzenesulphinate, melting point 312-320°C (decomposition).

The 6-(p-bromo- α -methylstyryl)-1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene used as the starting material can be prepared as follows:

50 g of [1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)ethyl]-triphenylphosphonium bromide are heated at reflux for 3 hours with 13.9 g of p-bromo-benzaldehyde in 400 ml of butylene oxide. The mixture is cooled, poured into 500 ml of methanol/water (6:4) and extracted three times with hexane. The organic phase is washed twice with water, dried over sodium sulphate and evaporated. The thus-obtained yellow-orange oil is recrystallized from ethyl acetate and gives 14.5 g of 6-(p-bromo- α -methylstyryl)-1,2,3,4-tetramethylnaphthalene in the form of colourless crystals, melting point 133-136°C.

20

Example 6

8.5 g of the sodium sulphinate obtained according to Example 5 are suspended in 350 ml of absolute methylene

chloride and treated while cooling with ice with a solution of 4.6 g of triethyloxonium tetrafluoroborate in 20 ml of methylene chloride. The mixture is stirred at +5°C for 2 hours, the precipitate is filtered off under suction, back-washed with methylene chloride and the filtrate is evaporated. The colourless oil is filtered over silica gel using hexane/ether 4:1 for the elution and gives, after crystallization from hexane/ether, 4.8 g of ethyl p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]benzenesulphinate in the form of colourless crystals, melting point 99-101°C.

Example 7

2.5 g of the sodium sulphinate obtained according to Example 5 are suspended in 60 ml of absolute dimethylformamide and treated with 1.0 g of ethyl iodide. The mixture is stirred for about a further 6 hours until a clear, yellowish solution is obtained. This solution is diluted with a large amount of water and extracted with ethyl acetate. The organic phase is washed several times with water, dried over sodium sulphate and evaporated. After recrystallization from hexane/ethyl acetate, there are obtained 1.9 g of ethyl p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]phenylsulphone in the form of colourless crystals, melting point 158-161°C.

In analogy to the procedure described above,

from sodium p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]benzenesulphinate and methyl iodide there is obtained methyl p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]phenylsulphone, melting point 176-178°C;

from sodium p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]benzenesulphinate and allyl bromide there is obtained allyl p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]phenylsulphone, melting point 140-141°C;

from sodium p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]benzenesulphinate and 2,2,2-trifluoroethyl iodide there is obtained 2,2,2-trifluoroethyl p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]phenylsulphone, melting point 158-159°C.

Example 8

18.1 g of [1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)ethyl]-triphenylphosphonium bromide

are heated at reflux for 3.5 hours with 5.0 g of p-
-ethylsulphonyl-benzaldehyde in 250 ml of butylene oxide.
The mixture is cooled, poured into 500 ml of methanol/
water (6:4) and extracted three times with hexane. The
5 organic phase is washed with water, dried over sodium sulphate
and evaporated. The crude product is filtered over silica
gel using hexane/ethyl acetate (1:1) for the elution and
recrystallized from hexane/ethyl acetate. There are
obtained 9.2 g of ethyl p-[2-(5,6,7,8-tetrahydro-5,5,8,8-
10 -tetramethyl-2-naphthyl)propenyl]phenylsulphone in the form
of colourless crystals, melting point 158-161°C.

The p-ethylsulphonyl-benzaldehyde used as the
starting material can be prepared as follows:

7.8 g of sodium hydride (50% suspension in mineral
15 oil) are washed with absolute pentane, dried in a water-
-jet vacuum and suspended in 100 ml of dimethylformamide.
11.3 g of ethyl mercaptan are added dropwise thereto while
cooling with ice, the mixture is stirred at room temperature
for 1 hour and subsequently a solution of 25.0 g of 4-
20 -bromobenzaldehyde in 100 ml of dimethylformamide is added
dropwise thereto. After 10 minutes, the mixture is poured
on to ice and extracted with ethyl acetate. The organic
phase is washed with 2N hydrochloric acid and water, dried
over sodium sulphate and evaporated. After filtration of

the oily residue over silica gel using hexane/ether (4:1) for the elution, there are obtained 17.5 g of 4-thioethylbenzaldehyde as a thin, light yellow oil.

10 g of 4-thioethylbenzaldehyde are dissolved in
5 150 ml of methylene chloride and treated portionwise with 22 g of m-chloroperbenzoic acid while cooling with ice. The mixture is diluted with methylene chloride, extracted twice with ice-cold potassium carbonate solution and water, dried over sodium sulphate and evaporated. After recrystal-
10 lization from hexane/ether, there are obtained 9.1 g of 4-ethylsulphonyl-benzaldehyde in the form of colourless crystals, melting point 107-109°C.

Example 9

In analogy to the procedure described in Example 8,
15 from 1-(1,1,3,3-tetramethyl-5-indanyl)ethyl-triphenyl-phosphonium bromide and 4-ethylsulphonylbenzaldehyde there is obtained ethyl p-[2-(1,1,3,3-tetramethyl-5-indanyl)propenyl]phenylsulphone, melting point 125-127°C;
20 from [1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)ethyl]-triphenylphosphonium bromide and

4-n-propylsulphonyl-benzaldehyde there is obtained propyl p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]phenylsulphone, melting point 151-152°C;

5 from [1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)ethyl]-triphenylphosphonium bromide and 4-isopropylsulphonylbenzaldehyde there is obtained isopropyl p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]phenylsulphone, melting
10 point 146-147°C;

from [1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)ethyl]-triphenylphosphonium bromide and 4-isobutylsulphonylbenzaldehyde there is obtained 1-methylpropyl p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]phenylsulphone,
15 melting point 143-144°C;

from [1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)ethyl]-triphenylphosphonium bromide and 4-(2-hydroxyethylsulphonyl)-benzaldehyde there
20 is obtained 2-[[p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]phenyl]sulphonyl]-ethanol, melting point 131-133°C;

from [1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-
-naphthyl)ethyl]-triphenylphosphonium bromide
and 4-ethylthio-benzaldehyde there is obtained
ethyl p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-
5 -2-naphthyl)propenyl]phenylsulphide, melting point
88-89°C;

from [1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-
-naphthyl)ethyl]-triphenylphosphonium bromide and
4-methylthiobenzaldehyde there is obtained methyl
10 p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-
-naphthyl)propenyl]phenylsulphide, melting point
119-120°C.

The benzaldehyde derivatives can be prepared as
described in Example 8 by reacting p-bromobenzaldehyde
15 with the corresponding mercaptan and subsequently oxidizing
the reaction product with m-chloroperbenzoic acid.

Example 10

6.4 g of ethyl p-[2-(5,6,7,8-tetrahydro-5,5,8,8-
-tetramethyl-2-naphthyl)propenyl]phenylsulphide are
20 dissolved in 150 ml of methylene chloride and treated at
0°C within 6 hours with 3 g of m-chloroperbenzoic acid.
The mixture is stirred at 0°C for a further 2 hours, diluted

with methylene chloride, extracted twice with ice-cold potassium carbonate solution and water, dried over sodium sulphate and evaporated. After chromatography on silica gel using hexane/ethyl acetate (4:1) for the elution and
5 crystallization from hexane/ethyl acetate, there are obtained 3.1 g of ethyl p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]phenylsulphoxide, melting point 148-150°C.

In analogy,

10 from methyl p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]phenylsulphide and m-chloroperbenzoic acid there is obtained methyl p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl[propenyl]phenylsulphoxide, melting point
15 155-156°C;

and from

methyl p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]phenylsulphoxide and m-chloroperbenzoic acid there is obtained methyl
20 p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]phenylsulphone, melting point 176-178°C.

Example 11

6.0 g of 2-[[p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]phenyl]sulphonyl]ethanol are dissolved in 150 ml of tetrahydrofuran and, after the addition of 1 ml of pyridine, the mixture is treated slowly with 1.7 g of phosphorus tribromide while cooling with ice. After 15 minutes, the mixture is poured into ice/water and extracted with ethyl acetate. The organic phase is washed with water, dried over sodium sulphate and evaporated. The thus-obtained brownish oil is dissolved in 200 ml of tetrahydrofuran and, after the addition of 70 ml of triethylamine, the mixture is warmed to 60°C for 6 hours. The mixture is poured into ice/water and extracted with ethyl acetate. The organic phase is washed with water, dried and evaporated. After filtration over silica gel using hexane/ethyl acetate (4:1) for the elution and crystallization from hexane/ethyl acetate, there are obtained 2.5 g of vinyl p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]phenylsulphone, melting point 130-132°C.

Example 12

4.5 g of 2-[[p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]phenyl]sulphonyl]ethanol are dissolved in 50 ml of acetonitrile and treated with

4 g of triphenylphosphine and 10 ml of carbon tetrachloride. After boiling at reflux for 4 hours, a further 2 g of triphenylphosphine and 2 ml of carbon tetrachloride are added thereto and the mixture is heated at reflux for a
5 further 3 hours. The mixture is cooled, poured into water, extracted with ethyl acetate, dried and evaporated. After chromatography on silica gel using hexane/ethyl acetate (4:1) for the elution and crystallization from pentane/ether, there are obtained 2.2 g of 2-chloroethyl p-[2-(5,6,7,8-tetra-
10 hydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]phenylsulphone, melting point 136-138°C.

Example 13

5.3 g of methyl p-[2-(5,6,7,8-tetrahydro-5,5,8,8-
-tetramethyl-2-naphthyl)propenyl]phenylsulphone are
15 dissolved in 100 ml of absolute tetrahydrofuran and treated at -75°C with 9 ml of a 2 molar solution of butyl lithium in hexane. After stirring at -75°C for 30 minutes, 1.8 g of ethyl chloroformate are added thereto and the mixture is stirred at room temperature for a further 2 hours. The
20 mixture is poured into ice/water, extracted with ethyl acetate, dried and evaporated. After filtration over silica gel using hexane/ethyl acetate (4:1) for the elution and crystallization from hexane/ethyl acetate, there are obtained 2.5 g of ethyl [[p-[2-(5,6,7,8-tetrahydro-5,5,8,8-
25 -tetramethyl-2-naphthyl)propenyl]phenyl]sulphonyl]acetate, melting point 117-118°C..

Example 14

99 g of [1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-
-2-naphthyl)ethyl]-triphenylphosphonium bromide are heated
at reflux for 40 hours with 25.2 g of S-(p-formylphenyl)-
5 dimethylthiocarbamate in 1 l of butylene oxide. The
mixture is cooled, poured into 1 l of methanol/water (6:4)
and extracted three times with hexane. The organic phase
is washed with water, dried over sodium sulphate and
evaporated. The crude product is filtered over silica gel
10 using hexane/ethyl acetate (4:1) for the elution and
recrystallized from ethyl acetate/hexane. There are obtained
39 g of S-[p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-
-2-naphthyl)propenyl]phenyl]dimethylthiocarbamate in the
form of colourless crystals, melting point 107-109°C.

15 The S-(p-formylphenyl)dimethylthiocarbamate
(melting point 78-80°C) used as the starting material can
be prepared from p-hydroxybenzaldehyde via O-(p-formyl-
phenyl)dimethylthiocarbamate (melting point 94-96°C)
according to the procedure described by M.S. Newmann and
20 H.A. Karnes in J. Org. Chem. 31, 3980 (1966).

Example 15

500 mg of lithium aluminium hydride are suspended
in 10 ml of tetrahydrofuran and treated dropwise while

cooling with ice with a solution of 5 g of S-[p-[2-(5,6,7,8-
-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]phenyl]-
dimethylthiocarbamate in 10 ml of tetrahydrofuran. After
stirring at room temperature for 2 hours, the excess
5 lithium aluminium hydride is destroyed by the dropwise
addition of water while cooling with ice and, after
acidifying the solution with 1N hydrochloric acid, the
mixture is extracted with ether. The ether phase is washed
neutral with water, dried over sodium sulphate and
10 evaporated. There are obtained 3.5 g of p-[2-(5,6,7,8-
-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]thio-
phenol as a colourless oil which is very sensitive to
oxidation and which can be crystallized from hexane/ether,
melting point 97-98°C.

15

Example 16

500 mg of sodium hydride (50% suspension in mineral
oil) are washed with absolute pentane, dried in a water-
-jet vacuum and suspended in 10 ml of dimethylformamide.
While cooling with ice there is added dropwise thereto a
20 solution of 3.3 g of p-[2-(5,6,7,8-tetrahydro-5,5,8,8-
-tetramethyl-2-naphthyl)propenyl]thiophenol in 5 ml of
dimethylformamide. After stirring at 0°C for 1 hour, there
are added dropwise thereto 3 g of ethyl iodide, the
mixture is left to come to room temperature and stirred for

5 a further 3 hours. The solution is poured into ice and extracted with ether. The organic phase is washed with 2N hydrochloric acid and water, dried over sodium sulphate and evaporated. The crude product is filtered over silica gel using hexane/ethyl acetate (9:1) for the elution and recrystallized from hexane. There are obtained 2.7 g of ethyl p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]phenylsulphide, melting point 88-89°C.

Example 17

10 3.5 g of p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]thiophenol are dissolved in 20 ml of dimethylformamide and treated with 4 g of methyl acrylate. After the addition of a few drops of triethylamine, the mixture is stirred at 60°C for 2 hours. After
15 cooling, the mixture is poured into ice/water, extracted with ether, washed with water, dried and evaporated. The crude product is filtered over silica gel using hexane/2% ethyl acetate for the elution and crystallized from hexane/ether. There are obtained 3.1 g of methyl 3-[[p-
20 -[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-propenyl]phenyl]thio]propionate, melting point 90-92°C.

Oxidation of the product obtained according to the preceding paragraph with m-chloroperbenzoic acid yields

(66)

methyl 3-[[p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]phenyl]sulphonyl]propionate, melting point 118-120°C.

Example 18

5 3.9 g of ethyl p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]phenylsulphone are dissolved in 20 ml of tetrahydrofuran and treated at -78°C with 5.5 ml of a 2 molar solution of butyl lithium in hexane. After 15 minutes, 370 mg of methyl acetate are
10 added thereto. After stirring at -78°C for 30 minutes, a further 2.75 ml of the butyl lithium solution are added thereto and, after 15 minutes, the mixture is treated with 185 mg of methyl acetate. After a further 30 minutes, the same procedure is repeated by the addition of 1.4 ml
15 of butyl lithium solution and 93 mg of methyl acetate. The mixture is left to come to room temperature, poured into ice/water and extracted with ether. After drying and evaporation of the organic phase, the residue is crystallized from ethyl acetate/hexane and there are
20 obtained 2.6 g of 3-[[p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]phenyl]sulphonyl]-2-butanone, melting point 139-141°C.

In analogy to the procedure described above, from methyl p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]phenylsulphone and methyl acetate there is obtained 1-[[p-[2-(5,6,7,8-tetrahydro-5,5,8,8-
5 -tetramethyl-2-naphthyl)propenyl]phenyl]sulphonyl]-1-propanone, melting point 140-141°C.

Example 19

5 g of sodium p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]benzenesulphinate are
10 suspended in 150 ml of benzene and treated with 1.3 g of chloromethyl methyl ether. After heating to 85°C for 8 hours, the solvent is removed by evaporation and the oily residue is chromatographed on silica gel using hexane/
ethyl acetate (9:1) for the elution. After recrystallization
15 from hexane/ethyl acetate, there are obtained 1.1 g of methyl [[p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]phenyl]sulphonyl]methyl ether, melting point 154-156°C.

Example 20

20 4 g of sodium p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]benzenesulphinate are suspended in a mixture of 80 ml of ethanol and 750 mg of acetic acid. The mixture is treated with 750 mg of

methyl vinyl ketone and stirred at room temperature for 20 hours. Thereafter, the mixture is washed with water, extracted with ether, dried and evaporated. After recrystallization from hexane/ethyl acetate, there are
5 obtained 3.5 g of 4-[[p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propenyl]phenyl]sulphonyl]-2-butanone, melting point 135-136°C.

Example A

An ointment containing 1% of active substance can
10 be manufactured from the following ingredients:

	Active substance, e.g. ethyl p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-propenyl]phenylsulphone	1.0 g
	Vaseline, white	35.0 g
15	Wax, white	4.0 g
	Paraffin oil, viscous	18.0 g
	DEHYMULS E *	7.0 g
	Benzoic acid	0.2 g
	Water, deionized	ad 100.0 g

20 * high molecular aliphatic ester; supplier:
Deutsche Hydrierwerke

Example B

An ointment containing 0.1% of active substance can be manufactured from the following ingredients:

5	Active substance, e.g. ethyl p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-propenyl]phenylsulphone	0.1 g
	Vaseline, white	35.0 g
	Wax, white	10.0 g
	Paraffin oil, viscous	18.0 g
10	DEHYMULS E	7.0 g
	Benzoic acid	0.2 g
	Water, deionized	ad 100.0 g

Example C

15 A suspension ointment can be manufactured from the following ingredients:

	Active substance, e.g. ethyl p-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-propenyl]phenylsulphone	0.3 g
	Paraffin oil, viscous	36.7 g
20	Vaseline, white	45.0 g
	LUNACERA M *	15.0 g
	Castor oil, solid	3.0

* hydrocarbon wax; supplier:
Luneburger Wachsbleiche

Claims

No English translation of the claims is provided herewith since the Letters Patent already contain an English version of the claims.