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(54) Benævnelse: **CANNABINOIDCARBOXYLSYRER, SALTE AF CANNABINOIDCARBOXYLSYRER, FREMSTILLING OG ANVENDELSE DERAF**

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CROMBIE ET AL.: J. CHEM. RESEARCH, 1977, Seiten 1301-1345, XP002690047, in der Anmeldung erwähnt
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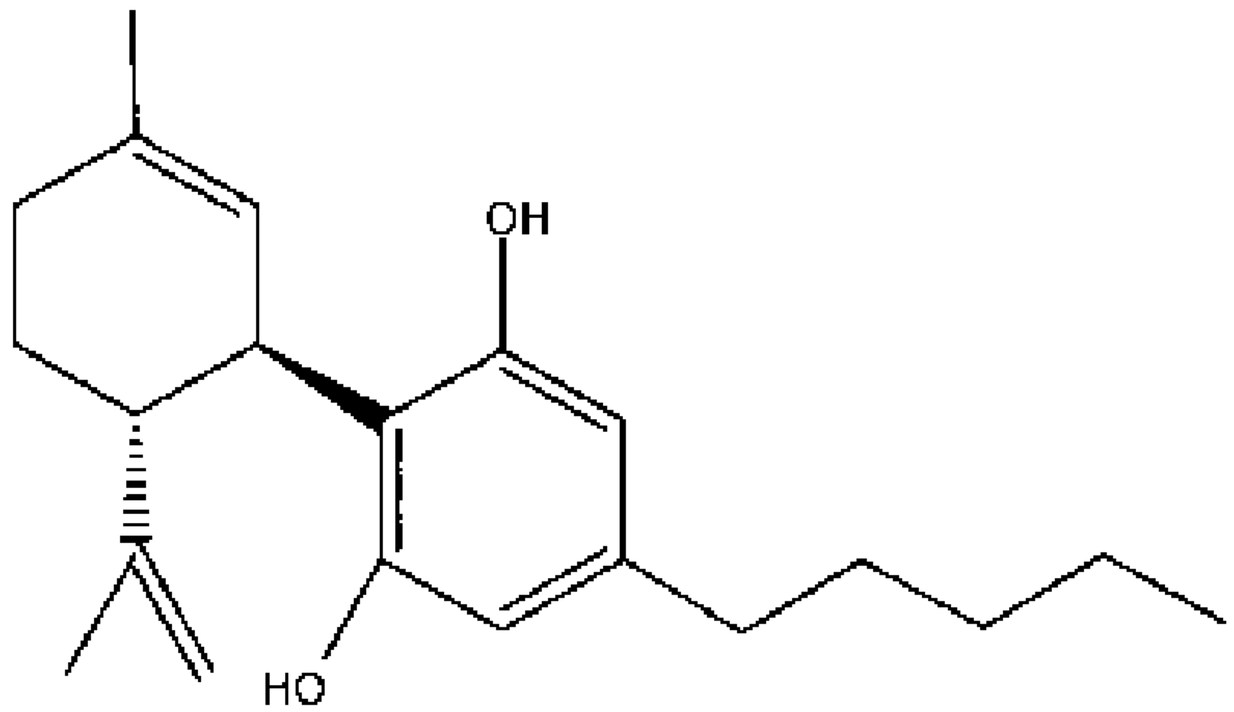
CANNABINOID CARBOXYLIC ACIDS, SALTS OF CANNABINOID CARBOXYLIC ACIDS, AND THE PRODUCTION AND USES OF SAME

Technical field

The invention relates generally to salts of cannabinoid carboxylic acids, methods for the manufacture thereof and uses thereof.

State of the art

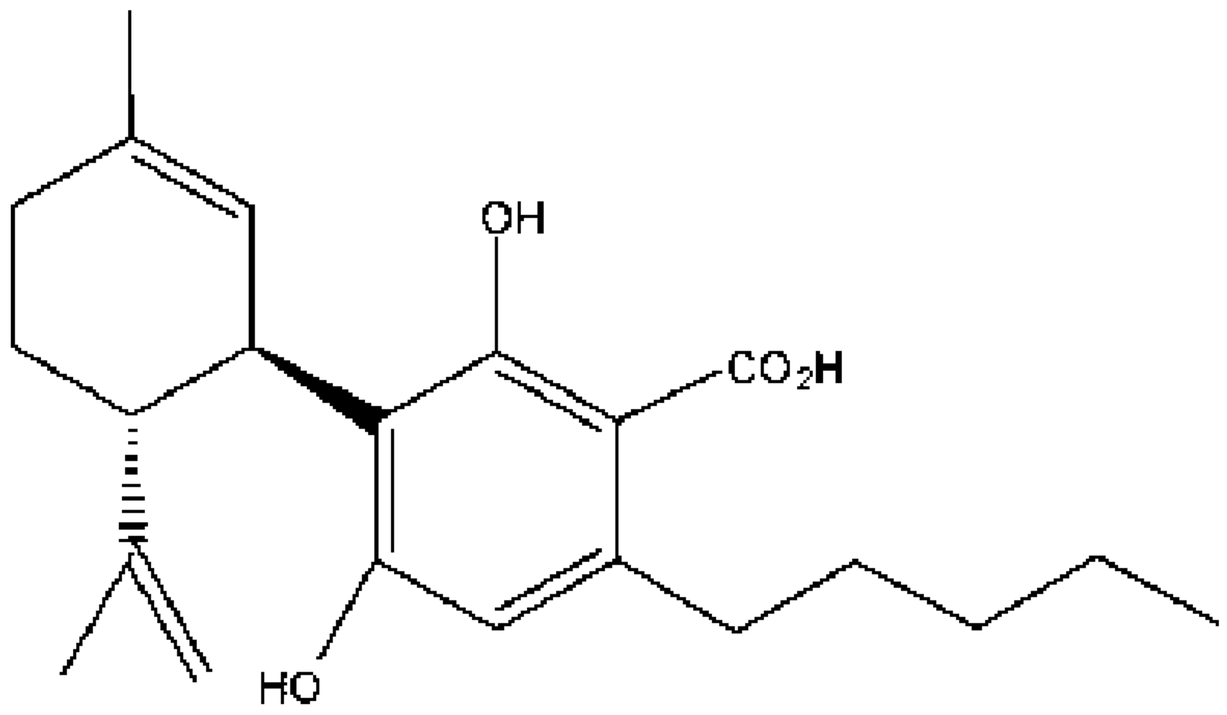
Cannabinoids occur in the hemp plant Cannabis sativa in the form of their carboxyl derivatives, the cannabinoid carboxylic acids, from which the so-called “neutral cannabinoids” are derived through decarboxylation, i.e. elimination of CO_2. Thus for example cannabidiol (CBD - (I)) is formed through decarboxylation of cannabidiolic acid (CBDA - (II)).



(I)

(-)-CBD

2-((1R,6R)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enyl)-5-pentylbenzene-1,3-diol

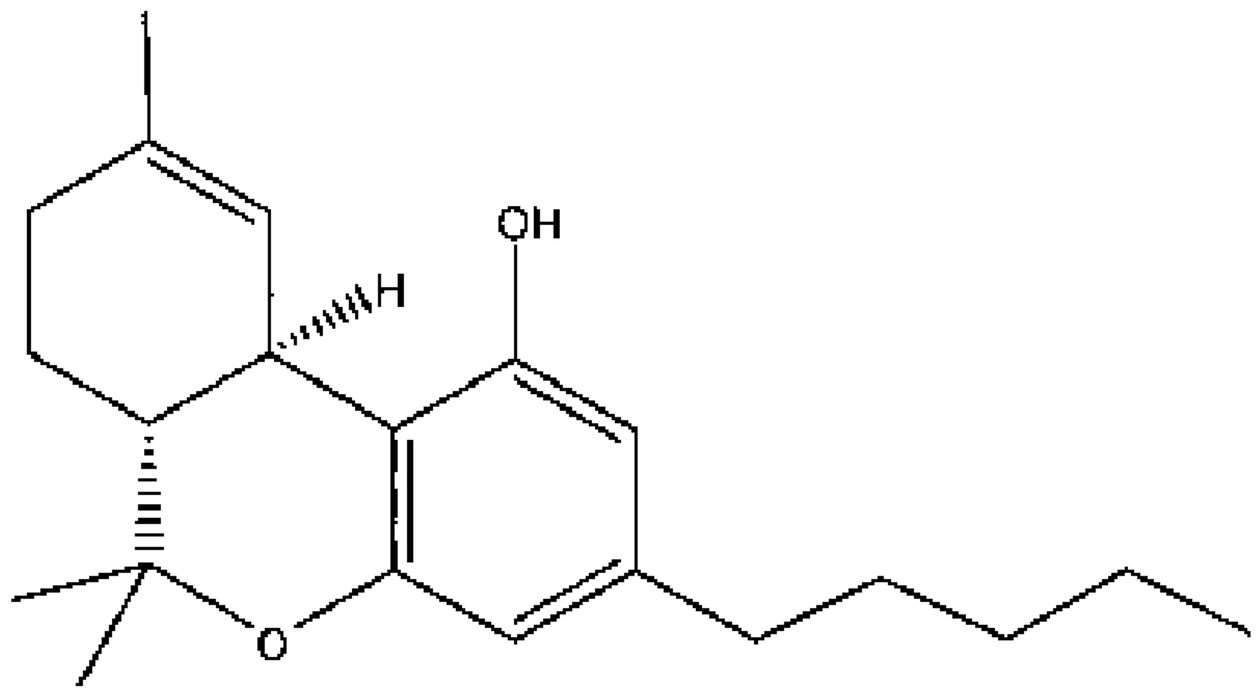


(II)

Cannabidiolic acid (CBDA)

2,4-dihydroxy-3-((1R,6R)-3-methyl-6-(prop-1-en-2-yl)-cyclohex-2-enyl)-6-pentylbenzoic acid

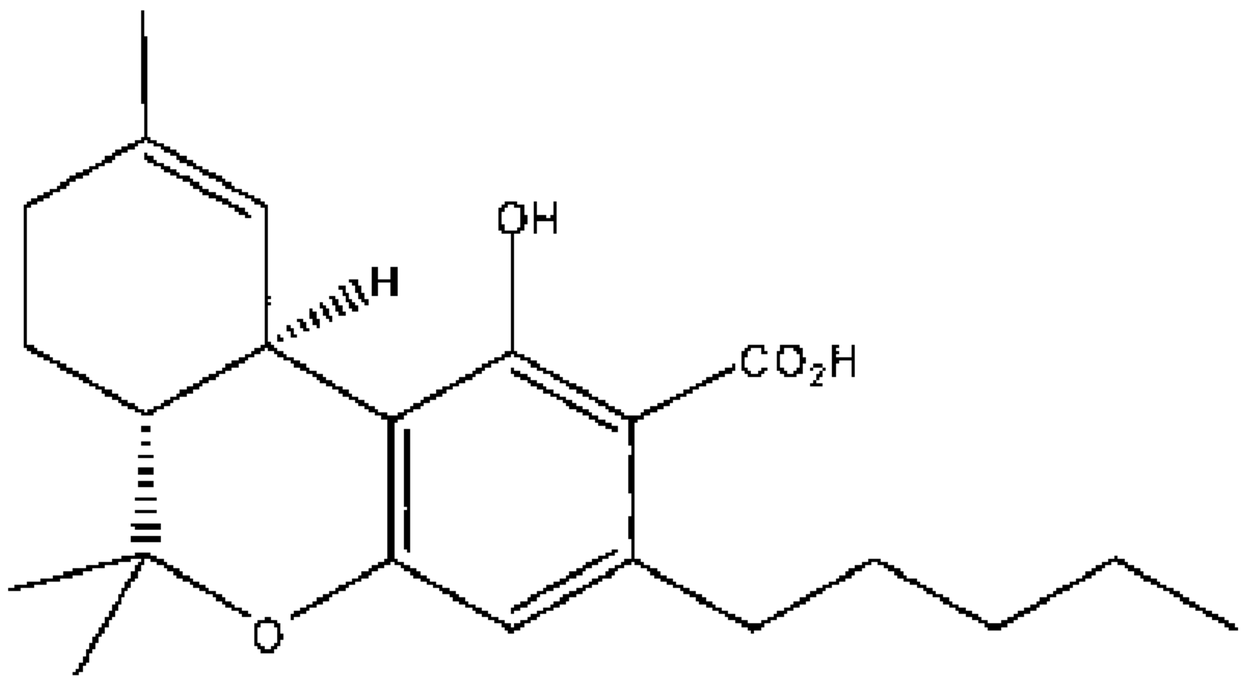
Δ^9-tetrahydrocannabinol (Δ^9-THC-dronabinol - (III)) is formed through decarboxylation from the positionally isomeric Δ^9-tetrahydrocannabinolic acids, Δ^9-tetrahydrocannabinolic acid A (THCA-A - (IV)) and Δ^9-tetrahydrocannabinolic acid B (THCA-B - (V)).



(III)

(-)-Δ^9-THC

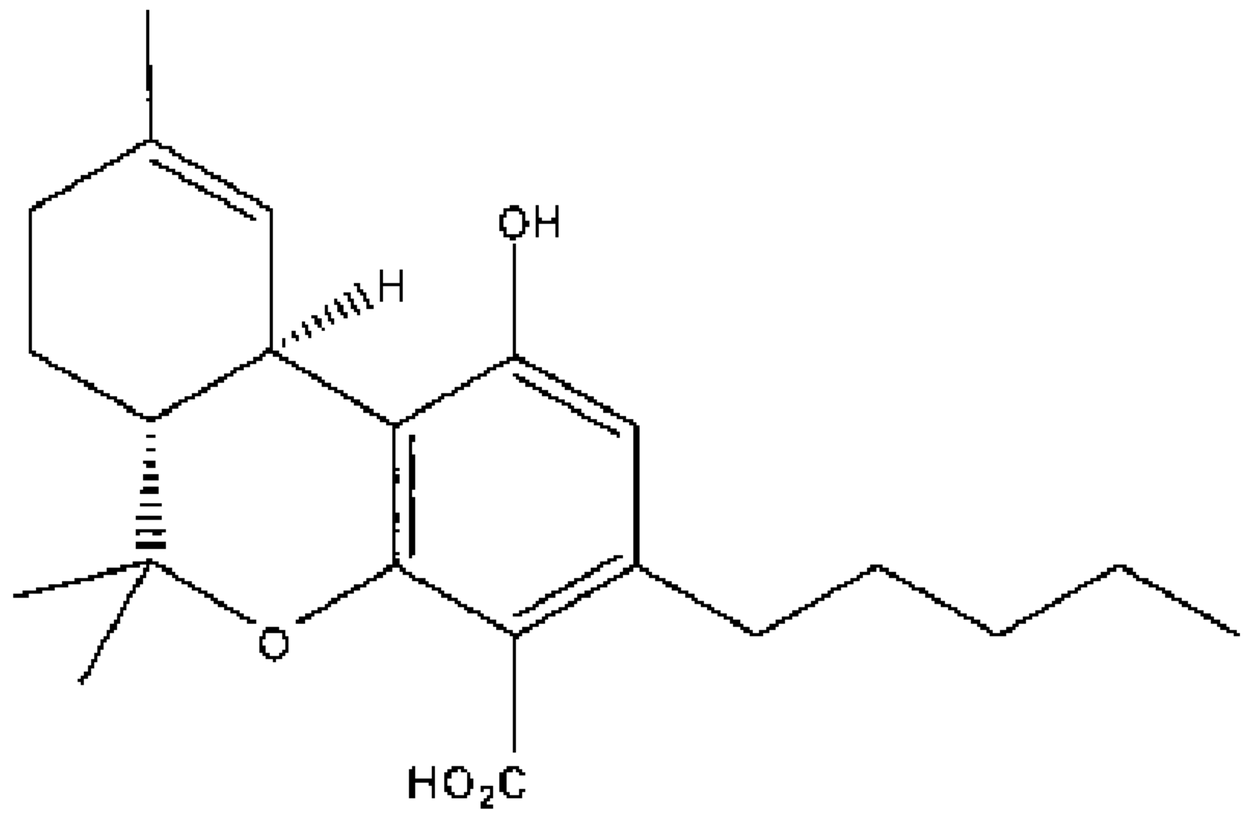
(6aR,10aR)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol



(IV)

Δ^9-tetrahydrocannabinolic acid A (THCA-A)

(6aR,10aR)-1-hydroxy-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromene-2-carboxylic acid,

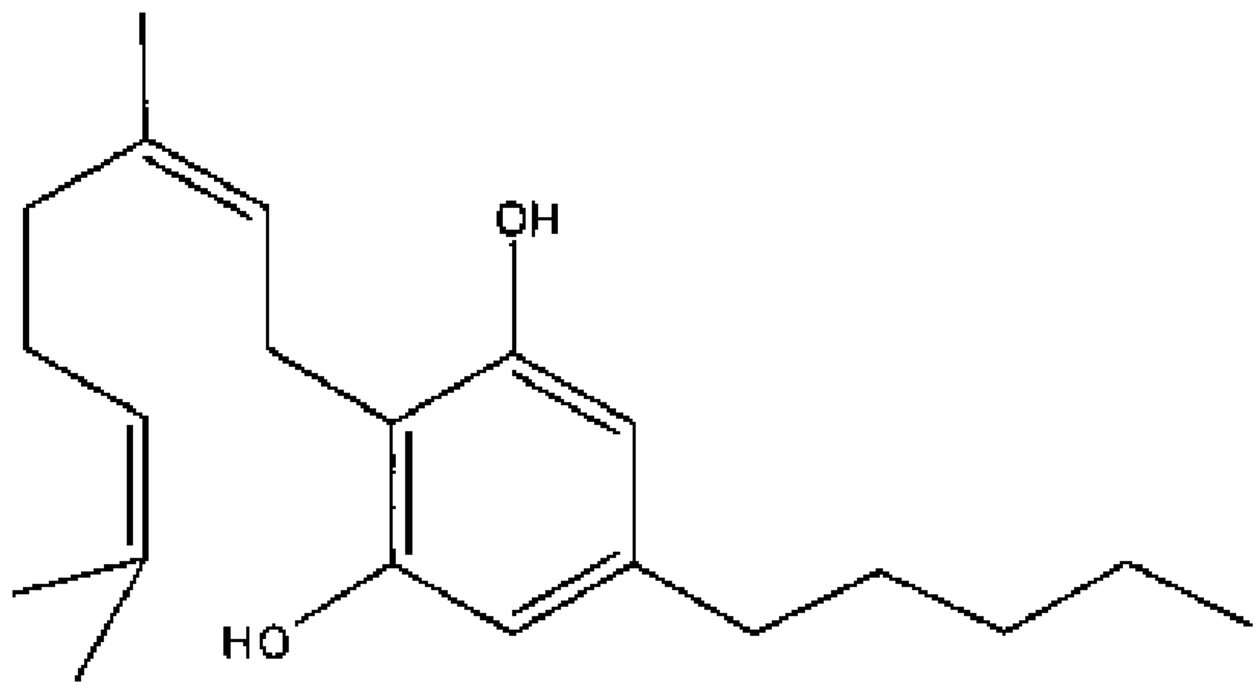


(V)

Δ^9-tetrahydrocannabinolic Acid B (THCA-B)

(6aR,10aR)-1-hydroxy-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromene-4-carboxylic acid).

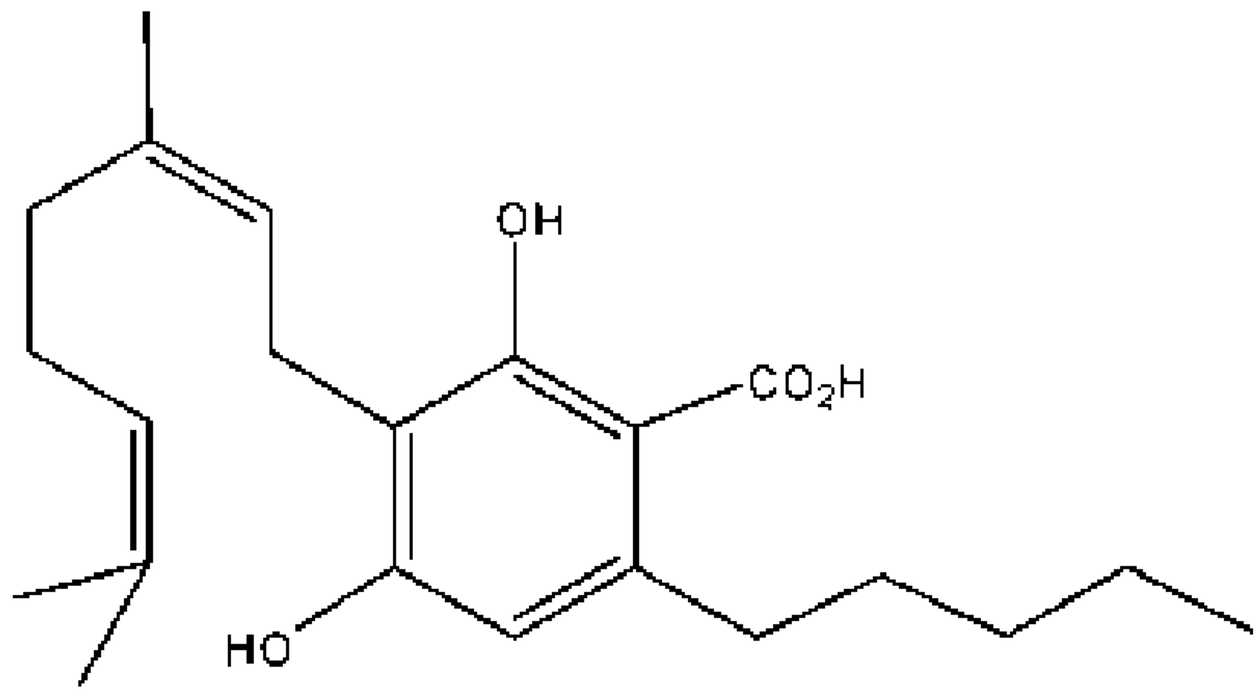
Cannabigerol (VI) is formed in this manner from cannabigerolic acid (CBGA - (VII)).



(VI)

Cannabigerol (CBG)

(Z)-2-(3,7-dimethylocta-2,6-dienyl)-5-pentylbenzene-1,3-diol



(VII)

Cannabigerolic acid (CBGA)

(Z)-3-(3,7-dimethylocta-2,6-dienyl)-2,4-dihydroxy-6-pentylbenzoic acid

[0005] The same applies analogously also to the naturally occurring trace cannabinoids such as for example Δ^8-tetrahydrocannabinol, cannabicyclol, cannabicitran, cannabielsoin or homologues of said cannabinoids. In the case of a closed pyran ring as with Δ^9-THC (III), two positionally isomeric carboxylic acids A and B are in each case possible. Both forms occur in nature (cf. e.g. R. Mechoulam et al., Tetrahedron, 1965, 21, 1223; F. Korte et al., Angew. Chem. Internatl. Ed., 1965, 4, 872 and R. Mechoulam et al., Tetrahedron Letters, 1969, 2339).

Previously compounds such as dronabinol (III) and homologues thereof had to be purified through laborious methods such as preparative chromatography. Thus US 4,025,516 discloses a process for the production of dronabinol through condensation of (+)-p-mentha-2,8-dien-1-ol with olivetol in the presence of BF_3 etherate. The synthesis of dronabinol from cannabidiolic acid esters in the presence of Lewis acids followed by hydrolysis is known from US 5,342,971. The production of dronabinol from tetrahydrocannabinol-rich cannabis followed by distillation and/or chromatography is described in the international patent application WO 00/25127. Finally DE 101 06 024 B4 discloses a process for the production of dronabinol wherein a) cannabidiol and/or cannabidiolic acid is isolated from plant materials, b) the cannabidiol that might be obtained through decarboxylation is cyclised to dronabinol in an organic or non-polar solvent in the presence of Lewis catalysts, c) this is isolated through a chromatographic process and d) the residue obtained from the eluate after distilling-off of the solvent is purified through vacuum distillation.

The production of crystallisable precursors such as the esters (e.g. of the 3,5-dinitrobenzoyl ester), crystallisation thereof and the subsequent saponification are relatively laborious and moreover associated with the risk of creating further impurities.

The reaction which gives rise to the formation of the neutral cannabinoids from the aforesaid cannabinoid carboxylic acids or salts thereof proceeds as a rule slowly at room temperature, but can be accelerated through heating and/or addition of catalysts, so that the CO_2 loss proceeds within a few minutes or practically immediately. This reaction can be controlled, such that it proceeds practically quantitatively and without the formation of further secondary products.

From the aforesaid it follows that pure cannabinoid carboxylic acids are practically ideal precursors for obtaining pure neutral cannabinoids therefrom. Therefore it would be a significant advance for the production of pure cannabinoids, to be able to provide a process which makes it possible to obtain and purify cannabinoid carboxylic acids economically.

Therefore the underlying object of the invention is to provide a method for the production of salts according to claim 1 which are as pure as possible, preferably crystalline salts of natural or synthetic cannabinoid carboxylic acids, from which pure neutral cannabinoids can be obtained in a simple manner

A further object consists in providing such a process, which can be performed with relatively little expenditure and is less susceptible to the formation of impurities.

Disclosure of the invention

The present invention achieves said object by providing a method for the production of crystalline and soluble salts of cannabinoid carboxylic acids according to claim 1 through manufacture of synthetic cannabinoid carboxylic acids in a chemical reaction or extraction of natural cannabinoid carboxylic acids from plant materials or cell cultures of Cannabis sativa and subsequent treatment with a suitable organic base, inorganic base and/or a suitable inorganic or organic salt in a suitable solvent.

EP 1 559 423 A1 discloses cannabinoid carboxylic acids, in particular for the treatment of skin diseases.

EP 2 314 580 A1 describes a method for the production of cannabinoids through saponification and decarboxylation of cannabinoid carboxylic esters, wherein a potassium salt of the cannabinoid carboxylic acid is used.

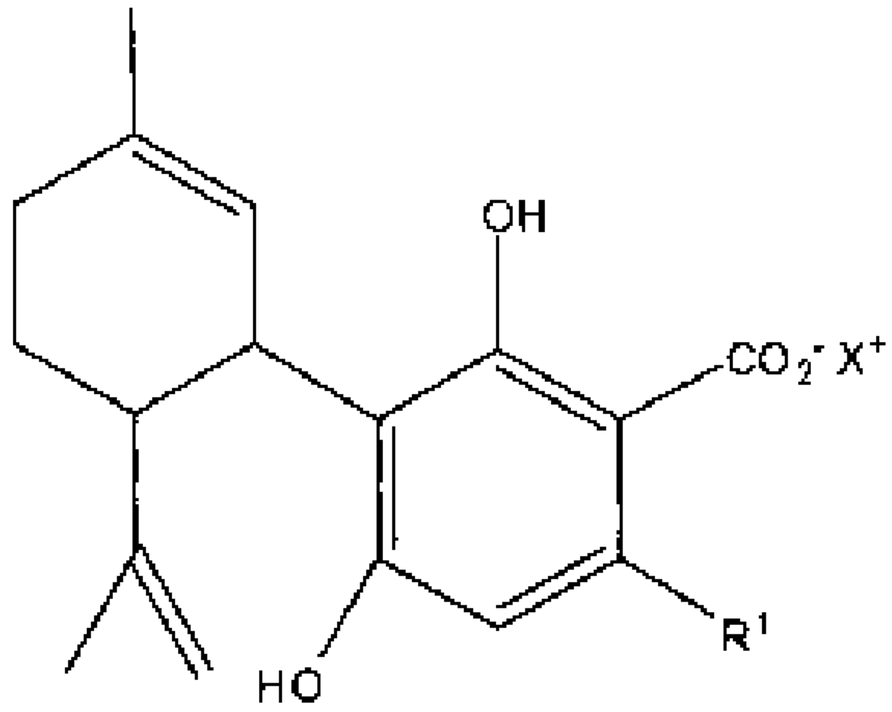
WO 03/064407 A2 discloses alkaline and alkaline earth salts of tetrahydrocannabinol acid, wherein the acid obtained therefrom is decomposed thermally.

The present invention achieves this object by providing a method for the production of amorphous and crystalline salts, in particular pure, preferably crystalline salts of cannabinoid carboxylic acids through production of synthetic cannabinoid carboxylic acids in a chemical reaction or extraction of natural cannabinoid carboxylic acids from plant materials or cell cultures of Cannabis sativa and subsequent treatment with a suitable organic base, inorganic base and/or a suitable inorganic or organic salt in a suitable solvent. Here pure is understood to relate to substance mixtures with a salt content of >90 wt.%.

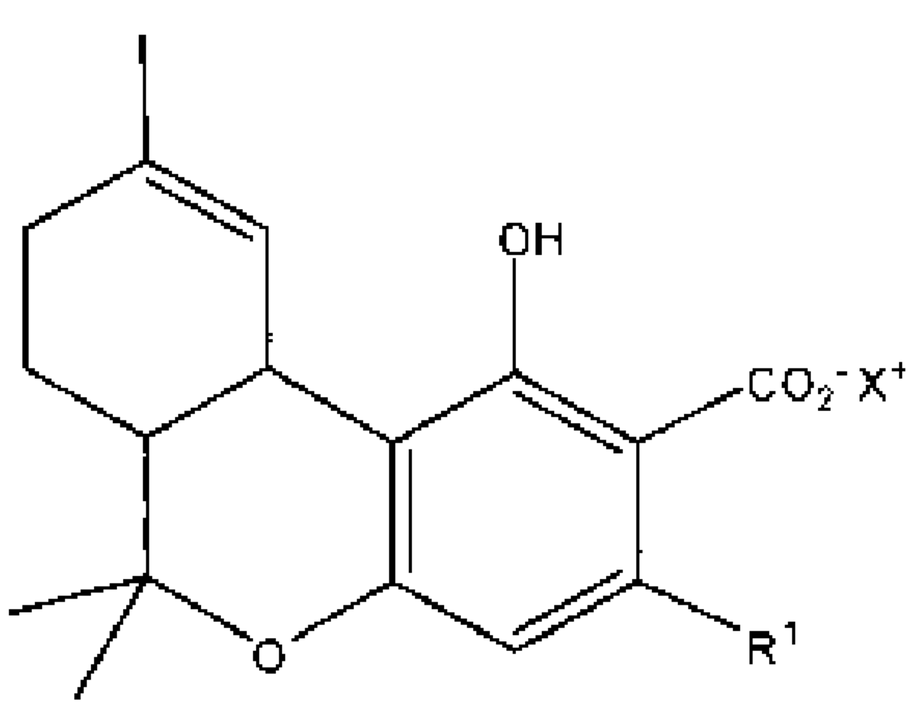
The present invention comprises the manufacture of natural or synthetic cannabinoid carboxylic acids and salts thereof (1) to (4), comprising all stereoisomers and their mixtures, in particular the manufacture for the first time of crystalline salts of cannabinoid carboxylic acids, their purification through recrystallisation and the obtaining of pure neutral cannabinoids therefrom.

Furthermore methods are disclosed, by means of which amorphous or crystalline salts can be obtained from cannabinoid carboxylic acids or amorphous or dissolved salts

of cannabinoid carboxylic acids can be converted into crystalline salts and by means of which pure neutral cannabinoids can be produced from pure cannabinoid carboxylic acids or salts thereof.



(1)



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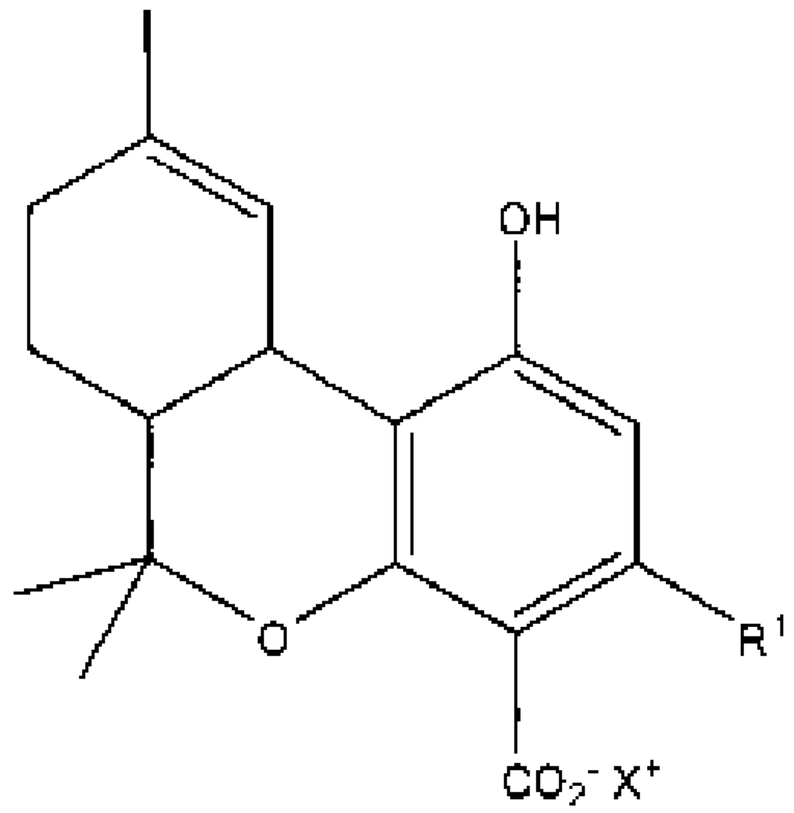

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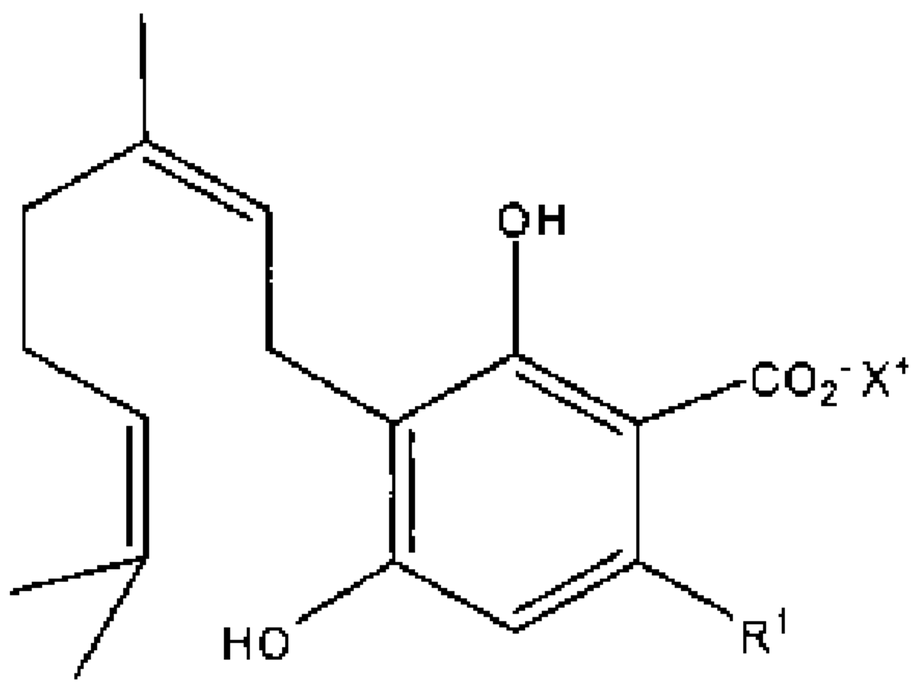


(4)

Therein $R^1$is a straight-chain, branched or cyclic hydrocarbon residue with one carbon atom up to 12 carbon atoms.

X^+ is preferably selected from the group consisting of NH_4^+ and primary, secondary, tertiary or quaternary organic ammonium ions with up to 48 carbon atoms, which can also carry other functional groups.

Examples of multivalent ammonium ions are N,N-dicyclohexylamine-H^+ and N,N-dicyclohexyl-N-ethylamine-H^+. X^+ can also be the hydrogenium cation of a pharmaceutical active substance with at least one basic nitrogen atom, e.g. morphine, methadone (or an enantiomer thereof) or hydromorphone.

The manufacture of pure, preferably crystalline salts of cannabinoid carboxylic acids comprises two steps. In a first step synthetic cannabinoid carboxylic acids are manufactured in a chemical reaction or natural cannabinoid carboxylic acids are extracted from plant material or cell cultures of Cannabis sativa.

In a second step the thus manufactured cannabinoid carboxylic acids or extracts rich in cannabinoid carboxylic acids are placed in a suitable solvent with a suitable organic base, a suitable inorganic base and/or a suitable inorganic or organic salt, so that the sparingly soluble salts of the cannabinoid carboxylic acids precipitate. These can be separated for example through filtration and, if necessary, purified through recrystallisation.

In a further step pure cannabinoids can be obtained from the thus manufactured pure, preferably crystalline salts.

This can be effected through displacement of the cannabinoid carboxylic acids by means of another acid, extraction of the pure cannabinoid carboxylic acids and subsequent thermal or catalytic decomposition, or through decomposition of the salts of cannabinoid carboxylic acids with primary, secondary or tertiary amines (but not quaternary ammonium salts), which can also take place with thermal or catalytic assistance.

The invention further comprises cannabinoid carboxylic acid-containing liquids and cannabinoid carboxylic acid salt-containing liquids for medicinal vaporisers.

Such liquids are preferred to the oral dronabinol preparations, which have the disadvantage of low and markedly varying bioavailability and moreover display low stability in relation to oxidation.

1. Manufacture and isolation of cannabinoid carboxylic acids

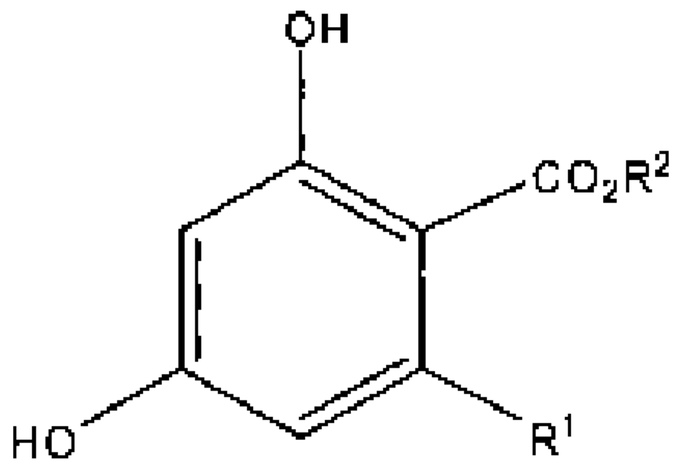
1.1 Synthetic manufacture of cannabinoid carboxylic acids

Method A:

Cannabinoid carboxylic acids can be manufactured synthetically through carboxylation from neutral cannabinoids according to processes known from the literature. In this regard see R. Mechoulam et al.: Chem. Communications, 1969, 343-344. Both natural and synthetic cannabinoids can be used as starting materials.

Method B:

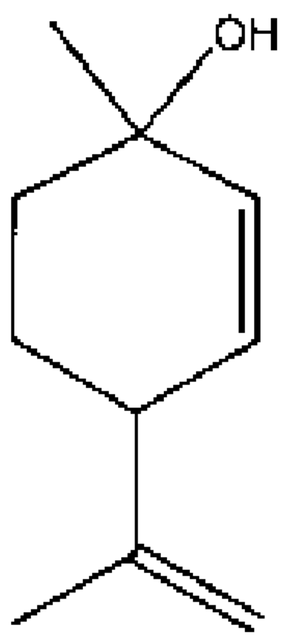
Synthetic cannabinoid carboxylic acids can be constructed through acid-catalysed terpenylation of alkylresorcyl esters (6-alkyl-2,4-dihydroxybenzoates) (5) and subsequent saponification of the esters, as described in Crombie et al.: J. Chem. Research pp. 1301-1345 (1977). In this terpenylation the use of the optically active compounds (6a) and (7a) respectively leads to the natural stereoisomers of the desired cannabinoid carboxylic acids and cannabinoids.



(5)

Here R^1 is defined as above. R^2 is H or a straight-chain or branched alkyl having up to 16 carbon atoms, which can carry further substituents such as phenyl, hydroxy, methoxy, ethoxy, halogen or nitrile.

In the terpenylation compounds of the type (5) react with terpenes such as p-menthadienol (6), verbenol (7) and geraniol (8).



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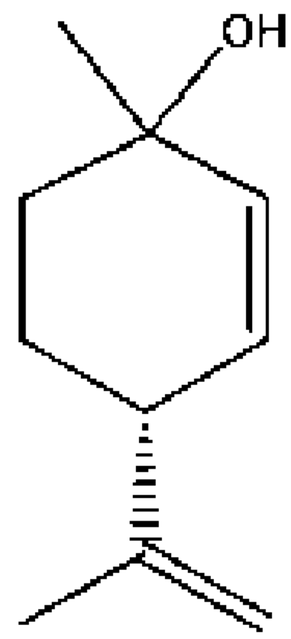
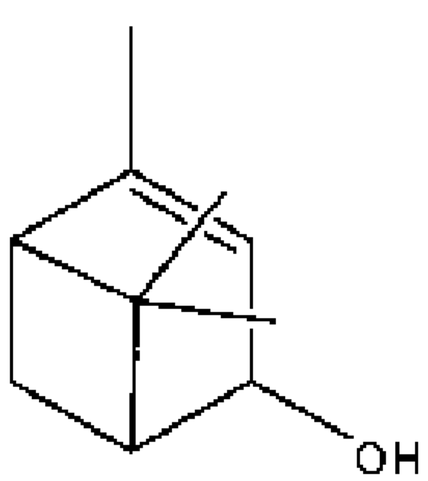


(6a)

(6a) = (4R)-1-methyl-4-(prop-1-en-2-yl)cyclohex-2-enol



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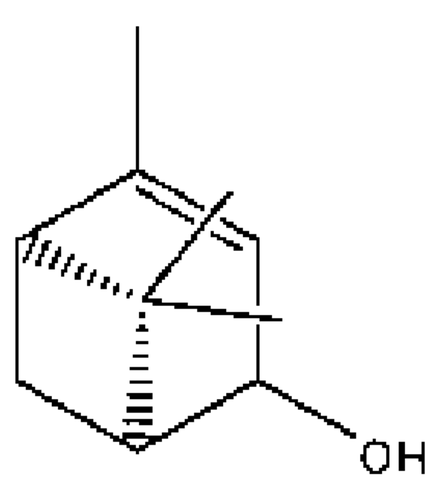
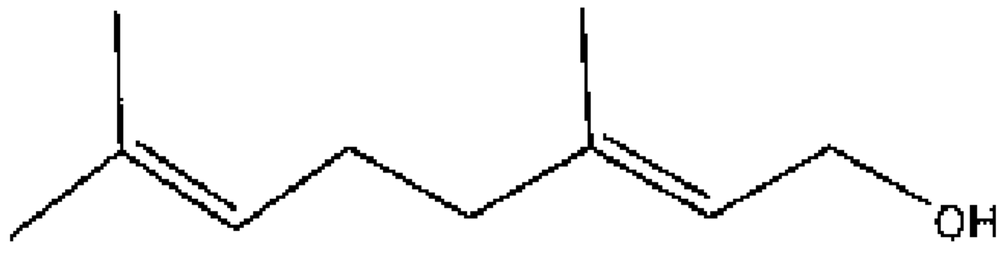


(7a)

(7a) = (1R,5R)-4,6,6-trimethylbicyclo[3.1.1]hept-3-en-2-ol



(8)

3,7-dimethylocta-2,6-dien-1-ol

Both Brönstedt acids and Lewis acids are suitable acids for the terpenylation step. Examples of suitable Brönstedt acids are: perchloric acid, hydrohalic acids (HF, HCl, HBr and HI), sulphuric acid, hydrogen sulphates, phosphoric acid and acid salts thereof, pyro- and polyphosphoric acids, organic carboxylic and sulphonic acids with one to 30 carbon atoms and one or more acidic groups, and acidic groups bound onto polymeric supports such as for example acidic ion exchangers and mixtures of the aforementioned acids. Formic acid, oxalic acid, trifluoroacetic acid and p-toluenesulphonic acid may be mentioned by name.

The invention includes, through reference, the entirety of the disclosure content of the European patent application EP 2 314 580 (Application No. 10 004 422.1 - 2117), at least regarding the procedures described therein for the acid-catalysed terpenylation for the production of the precursors of the salts according to the invention.

Examples of suitable Lewis acids are the cations of alkaline earth and earth metals and transition metals; the halogen compounds and other trivalent compounds of elements of the third main group such as boron trifluoride and other boron-halogen compounds and complexes thereof, aluminium halides such as anhydrous aluminium chloride; salts and halogen compounds of transition metals such as titanium tetrachloride, zinc chloride and zinc trifluoromethanesulphonate; halogen compounds of elements of the fourth and fifth and sixth main group such as for example tin tetrachloride, phosphorus trichloride, phosphorus pentachloride, phosphorus oxychloride, antimony pentafluoride, thionyl chloride and sulphuryl chloride, alone or mixed with other Lewis or Brönstedt acids, and positive centres such as montmorillonite bound onto polymer skeletons.

Further suitable reagents for performing the condensation are the acetals of N,N-dimethylformamide such as for example N,N-dimethylformamide dineopentyl acetal and other water-abstracting reagents, for example those which are used for the formation of amides and peptides, e.g. PPAA (T3P = propanephosphonic acid anhydride).

These reagents can be added as such to the reaction mixture or applied onto a support material such as for example aluminium oxide.

Suitable solvents for performing the terpenylation step are water, solvents immiscible with water or miscible with water such as for example hydrocarbons with up to 30 carbon atoms, halogenated hydrocarbons with up to 20 carbon atoms such as for example dichloromethane or chloroform, ethers such as for example 2-methyltetrahydrofuran, alcohols, carboxylic acids with up to 16 carbon atoms, amides with up to 20 carbon atoms, esters with up to 60 carbon atoms, carbon dioxide, sulphur dioxide, water, water with a phase transfer catalyst, the acidic catalysts themselves, and mixtures of the aforementioned solvents with one another.

To perform the process, an – as a rule – equimolar mixture of 6-alkyl-2,4-dihydroxybenzoic acids (5) and the relevant terpene in one of said solvents is treated with a catalytic, up to approx. equimolar quantity of acid and stirred at a temperature between minus 40 °C and plus 120 °C until the reaction has reached the desired degree (checking by means of thin layer chromatography or HPLC).

Next the acid is neutralised with an aqueous base such as aqueous sodium hydrogen carbonate, and the organic layer is separated off and evaporated. Cannabinoid carboxylic acid esters are thus obtained, which, as described by Crombie et al., can be saponified to the corresponding cannabinoid carboxylic acids (cannabinoid carboxylic acids).

Method C:

The cannabinoid carboxylic acids (II), (IV), (V) and (VII) and homologues thereof can also be constructed directly from 6-alkyl-2,4-dihydroxybenzoic acids (5: R^2 = H) and the corresponding terpenes. Here the same reagents and solvents are used as with the esters of the 6-alkyl-2,4-dihydroxybenzoic acids

Through construction from non-esterified 6-alkyl-2,4-dihydroxybenzoic acids the subsequent saponification step is avoided.

1.2 Extraction of cannabinoid carboxylic acids from natural plant material of *Cannabis sativa* or from cell cultures

The parts of Cannabis sativa (hemp) growing above ground and cell cultures of this species contain the cannabinoid carboxylic acids (II), (IV), (V) and (VII) and also further cannabinoid carboxylic acids and low homologues thereof in usable quantities. Advantageously a resin-rich extract of plant parts, such as can be obtained for example through the “Ice-o-later” process or through sieving-out of the resin glands, can be used for further concentration of the cannabinoid carboxylic acids.

Through extraction with a suitable solvent a cannabinoid carboxylic acid-rich extract can be obtained therefrom, in which, depending on the crop variety of Cannabis sativa, one of said cannabinoid carboxylic acids predominates.

For this, plant parts dried as necessary or cell cultures are contacted with a suitable solvent and thus respectively the cannabinoid carboxylic acids mainly stored on the outside of the cell are “washed” off or the cell cultures are extracted.

Expediently the desired cannabinoid carboxylic acids are concentrated in the solvent through the use of extract already containing cannabinoid carboxylic acid for the extraction of further plant material.

Advantageously the counter-current process is used for this, i.e. the cannabinoid carboxylic acid-containing extract is already contacted with fresh plant material and fresh solvent is contacted with already “washed” hemp.

Through cautious evaporation at low temperatures, preferably below 60 °C, the cannabinoid carboxylic acids can thus be concentrated in the crude extract

If necessary, this work is done under reduced pressure in order to lower the boiling point of the solvent.

i) Suitable solvents immiscible with water:

Hydrocarbons with up to 30 carbon atoms, including liquefied hydrocarbons gaseous in the normal state such as propane and/or butane, petroleum distillates such as petroleum ether, ligroin, kerosene, naphtha, halogenated hydrocarbons with up to 12 carbon atoms, carbon disulphide, esters and ethers with up to 16 carbon atoms, alcohols, ketones and nitriles with at least 4 and up to 12 carbon atoms, as well as mixtures of the solvents mentioned.

ii) Suitable solvents miscible with water

Water with basic additives, e.g. ammonia, alkylamines, hydroxylamine, hydrazine, water with detergents, lower alcohols with up to 4 carbon atoms, acetonitrile, propionitrile, acetone, as well as mixtures of the solvents mentioned.

iii) Also carbon dioxide and liquefied sulphur dioxide, liquefied ammonia, liquefied alkylamines, also with additions of the solvents mentioned under i) and ii).

From water-immiscible solvents the cannabinoid carboxylic acids can also be separated off from the neutral components through washing with aqueous alkali. For this an extract prepared with one of the solvents named under i) is contacted with an aqueous ammonia through stirring or shaking. The phases are then allowed to separate and the aqueous phase, which now contains the pre-purified cannabinoid carboxylic acids (largely freed from neutral components) in the form of their soluble salts, is separated off.

Through cautious acidification (neutralisation) with an acid the extracted cannabinoid carboxylic acids can be precipitated from this and, if appropriate, extracted with one of the solvents named under i).

Example:

100 g dried (or approx. 300 g fresh) flowering tops and leaves of Cannabis sativa (THC type of the “white widow” variety) are extracted with 1 l petroleum ether at <40 °C. Next the undissolved plant components are filtered out. This first extract is stirred with 0.5 l aqueous 0.1 molar potassium hydroxide solution, to which 5 g sodium sulphite can be added to protect against oxidation. This second, aqueous extract is separated off and treated with a solution of 5 g citric acid in 50 ml water, whereupon the cannabinoid carboxylic acids precipitate as oil. Through addition of 200 ml petroleum ether and stirring a third extract is now prepared. Separating-off of the organic phase and evaporation under reduced pressure at 40 °C yields 15.7 g of an oily residue, 80 % of which is a mixture of the Δ^9-THC acids A and B.

The crude cannabinoid carboxylic acids can be obtained through evaporation, preferably below 60 °C, from the extracts obtained with the solvents named under ii) and iii).

The cannabinoid carboxylic acids can be obtained from extracts obtained with water with basic additives through cautious acidification (neutralisation) and, if necessary, extracted with one of the solvents named under i).

Cannabinoid carboxylic acids from hemp extracts can also be separated off from non-acidic components by means of basic ion exchangers.

2. Crystalline salts of cannabinoid carboxylic acids

2.1 Precipitation of crystalline salts with suitable bases

If cannabinoid carboxylic acids or cannabinoid carboxylic acid-containing extracts in a suitable solvent are reacted with a suitable base, crystalline salts are formed, which can be separated off.

Suitable solvents are alcohols, esters, ethers, ketones, hydrocarbons, halogenated hydrocarbons and nitriles with up to 20 carbon atoms.

Suitable bases for the formation of crystalline salts are primary, secondary and tertiary organic amines with up to 48 carbon atoms such as for example dicyclohexylamine and ammonia. Further suitable organic bases are pharmaceutical active substances with at least one basic nitrogen atom in the molecule, e.g. morphine, hydromorphone (Palladon®), buprenorphine etc.

Procedure:

A quantity of base equivalent to the expected quantity of desired cannabinoid carboxylic acids is added with stirring to the solution of the cannabinoid carboxylic acids in a suitable solvent. Preferably work is done here with approx. 2 % to approx. 20 % solutions of cannabinoid carboxylic acids. This is allowed to crystallise overnight and the crystallisation is completed, if necessary, through cooling to approx. -10 °C. Next the precipitated crystalline slurry is suction-filtered/centrifuged off and rinsed with a small quantity of the same solvent as was used for the precipitation. The salt is then allowed to dry at <40 °C. It can be purified through suspension in one of the aforementioned solvents, digestion and suction-filtration of the undissolved matter. It can also be recrystallised from a suitable solvent, preferably a lower alcohol, nitrile, ketone, ester or ether with up to 4 carbon atoms.

Example:

15.7 g of an approx. 80 % mixture of Δ^9-THC acids A and B are dissolved in 150 ml isopropanol with stirring and 8.0 g dicyclohexylamine are added with stirring. 24 h stirring at 0 °C produces a thick white precipitate of the dicyclohexylamine salts of the cannabinoid carboxylic acids. After suction-filtration, washing with 50 ml cold isopropanol and drying, 18.7 g of dicyclohexylamine salt of the Δ^9-THC acids with a content of 91 % are obtained.

Precipitation of the dicyclohexylamine salt of CDBA from an isopropanolic industrial hemp extract

Example:

2 kg of flowering tops of industrial hemp (e.g. of the variety Fedora 19, but others are also possible) dried at below 30 °C are extracted in portions with cold (<15 °C) isopropanol using the counter-current process. The extract obtained is concentrated under reduced pressure at max. 40 °C to a volume of approx. 400 ml. This concentrate is treated with 12 g dicyclohexylamine and stirred for 24 h at 0 °C. The dicyclohexylamine salt of cannabidiolic acid crystallises and is suction-filtered off. Rinsing with 80 ml ice-cold isopropanol and drying under vacuum yields 22.4 g cream-coloured salt.

2.2 Precipitation of salts through addition of a suitable cation to a solution of cannabinoid carboxylic acids

To a solution of cannabinoid carboxylic acids in a suitable solvent is added an equivalent quantity of a base, which in the solvent used forms amorphous or soluble salts with the corresponding cannabinoid carboxylic acids, such as for example ammonia. Next the solution of a suitable primary, secondary, tertiary or quaternary ammonium salt or of a metal salt of the first, second, third, fourth or fifth main group, of a lanthanide metal or of a transition metal, e.g. silver, in a suitable solvent is added into the solution of the cannabinoid carboxylic acid salts. Suitable solvents are those named under 2.1.

Suitable primary, secondary, tertiary or quaternary ammonium salts are organic ammonium salts with up to 48 carbon atoms, which can also carry other functional groups.

The solvent and the ammonium salt or metal salt are selected such that the relevant cation forms a sparingly soluble precipitate with the anions of the cannabinoid carboxylic acids in the relevant solvent.

The corresponding sparingly soluble cannabinoid carboxylic acid salt precipitates and is isolated through suction-filtration or centrifugation.

2.3 Recrystallisation of cannabinoid carboxylic acid salts

Since the cannabinoid carboxylic acid salts are more stable in relation to decarboxylation than the free acids, the salts thus precipitated can be purified through recrystallisation. The same solvents can be used for the recrystallisation as for the precipitation. The crystallisation is preferably from a lower alcohol, ketone, nitrile, ester or ether with up to 8 carbon atoms. The addition of a catalytic quantity of complexing agent for metal cations, e.g. EDTA sodium or a crown ether, can increase the stability of the cannabinoid carboxylic acid salts during the recrystallisation procedure. This purification process has the advantage that it is considerably simpler to perform

compared with the processes conventionally used with cannabinoids, such as chromatography.

Example:

18.7 g dicyclohexylamine salt of Δ^9-THCA A and B with a content of 91 % Δ^9-THC acids in the cannabinoid fraction are dissolved with stirring in 150 ml boiling absolute ethanol and cooled immediately, after dissolution has occurred. Stir overnight at 0 °C to crystallise out. Suction-filter the white precipitate formed and wash with 50 ml cold absolute ethanol. Yield: 15.5 g pure-white salt with a content of >97 % Δ^9-THC acids (A and B) in the cannabinoid fraction.

This product is of sufficient purity to provide pharmaceutically usable dronabinol as per DAC 2003 after decarboxylation.

A further use of the cannabinoid carboxylic acid salts thus produced is as stable additives to dermatological products. For this, preferably salts of cannabinoid carboxylic acids which have been formed with bases toxicologically harmless or therapeutically active in man or animals are used. These salts need not be crystalline, but can also be used in amorphous form and be added to the dermatological products. They are characterised by increased stability (shelf life) compared with free cannabinoid carboxylic acids. A further stabilisation can be achieved through addition of metal complexing agents, e.g. EDTA sodium, which complex metal ions that catalyse the decarboxylation of cannabinoid carboxylic acid salts.

3. Obtaining of pure cannabinoids from salts of cannabinoid carboxylic acids

3.1 Manufacture of pure cannabinoids from cannabinoid carboxylic acid salts through displacement of the free cannabinoid carboxylic acids

Through addition of an acid to cannabinoid carboxylic acid salts the carboxylate anions are reprotonated and the free lipophilic acids can be extracted with a suitable solvent. Suitable solvents for this are those named under 1.2.i).

Suitable acids are water-soluble Brönstedt acids with a pK_a below 7, and carbonic acid (generated for example through passing of CO_2 into water).

Preferably readily volatile solvents are used which have a boiling point below 160 °C at normal pressure. After removal of the solvent through distillation, preferably at low temperature such as <60 °C, preferably <40 °C, the free cannabinoid carboxylic acids remain as residue.

Example:

15.0 g recrystallised dicyclohexylamine salt of the tetrahydrocannabinolic acids A and B are suspended in 200 ml water and overlayered with 200 ml petroleum ether. 3.0 g citric acid are now added and the mixture is stirred until the cannabinoid carboxylic acid salt has completely dissolved. The aqueous phase, which now contains the citrate of dicyclohexylamine, is separated off and discarded. The petroleum ether phase, which now contains the free Δ^9-tetrahydrocannabinolic acids, is successively washed once with 50 ml 1% citric acid and three times with 50 ml portions of water. After evaporation of the petroleum ether phase on the water-bath at 40 °C under reduced pressure 9.8 g amorphous residue of the two positionally isomeric Δ^9-tetrahydrocannabinolic acids remain.

3.1.1 Cannabinoids through thermal decomposition (decarboxylation) of cannabinoid carboxylic acids

Through heating to a temperature >60 °C, preferably over 100 °C, the free cannabinoid carboxylic acids are decarboxylated, i.e. they are converted into the corresponding neutral cannabinoids through release of carbon dioxide. This work is preferably done in vacuo or under an inert gas atmosphere, in order to prevent oxidation of the cannabinoids formed. If the work is done under a sufficient vacuum, preferably below 0.3 mbar, the product can be distilled immediately at a temperature of preferably over 140 °C. If the heating is performed in a current of gas, the resulting vapours of the neutral cannabinoids can be administered medicinally in an inhalation apparatus.

Example:

9.8 g Δ^9-tetrahydrocannabinolic acids (A and B) with a purity of 97.8 % determined by means of HPLC are heated for 30 min to 160 °C in a current of nitrogen. After carbon dioxide evolution has stopped, 8.4 g dronabinol with a purity of 97.6 % (HPLC) remain.

3.1.2 Cannabinoids through catalytic decomposition (decarboxylation) of cannabinoid carboxylic acids

Catalysts can accelerate the decarboxylation of cannabinoid carboxylic acids significantly, so that this practically instantaneously proceeds quantitatively. This was observed in the rapid onset of bubble formation (CO_2) in free cannabinoid carboxylic acids on metal surfaces such as steel. Suitable catalysts are elements of the transition metals in finely distributed form or with activated surfaces and also ions of transition metals. Conversely the deactivation of surfaces or the addition of complexing agents can be used, in order to stabilise cannabinoid carboxylic acids and salts thereof.

Example:

In a medicinal inhaler (e.g. "Vulcano") 0.05 ml of a 5 % ethanolic solution of pure Δ^9-tetrahydrocannibinolic acids (A and B) is applied onto the metal wire gauze of the vaporiser part. A current of hot gas at 230 °C is then allowed to pass through the vaporiser part for 60 s. Finely nebulised Δ^9-tetrahydrocannibinol of pharmaceutical purity for inhalation for medicinal use collects in the balloon (collector part).

3.2 Cannabinoids through decomposition of cannabinoid carboxylic acid salts

In the cold and at room temperature the salts of cannabinoid carboxylic acids are stable substances that can be stored undecomposed for years. Moreover crystalline salts of cannabinoid carboxylic acids can be particularly easily and effectively purified through recrystallisation. These properties can be exploited, in order to use them as quantitative and qualitative standards in analytical chemistry.

3.2.1 Thermal decomposition of cannabinoid carboxylic acid salts

The salts of cannabinoid carboxylic acids with primary, secondary and tertiary amines have a mobile hydrogenium ion (H^+) in the cation, which at elevated temperature is in perceptible equilibrium with the carboxylate anion of the cannabinoid carboxylic acid component. In the reprotonated state the cannabinoid carboxylic acids are readily accessible to decarboxylation to the corresponding neutral cannabinoids. Thus, if cannabinoid carboxylic acid salts of ammonia, primary, secondary and tertiary amines, hydrazine, hydroxylamine, guanidine and organic derivatives thereof are heated strongly, carbon dioxide is readily evolved and mixtures of the free amines and the neutral cannabinoids are formed. At elevated temperature, particularly in vacuo or in a current of gas, these are present in vapour form and can be used for example for inhalation.

Another application exists in the use of the salts of cannabinoid carboxylic acids, stable in the cold and at room temperature, as reference substances and standards for gas chromatography. This is particularly advantageous in cases where the cannabinoids formed are unstable, oxidation-sensitive substances, such as for example in the case of Δ^9-tetrahydrocannabinol.

In these cases a solution of a stable salt, e.g. the dicyclohexylamine salt of Δ^9-tetrahydrocannabinolic acid A or B, with a primary, secondary or tertiary amine is injected into the injector of the gas chromatograph. Because of the high temperature of the injection block (as a rule >230 °C) the salt immediately decomposes quantitatively into the neutral cannabinoid (in the case of the example Δ^9-tetrahydrocannabinol), the amine

and CO_2. The amine (in the case of the example dicyclohexylamine) is separated off by the chromatography system as separate peak and does not affect the quantification of the cannabinoid.

In a medicinal inhaler the decomposition of cannabinoid carboxylic acid salts in substance or solution with pharmaceutically active amines such as analgesics or local anaesthetics can be used for a combination therapy or to mask the tussive effect of cannabinoids such as dronabinol. The thermal decomposition of a salt of cannabinoid carboxylic acids with vaporisable pharmacologically active amines leads to both the neutral cannabinoid and also the amine component becoming nebulised and being available in the form of an aerosol for inhalation. The fine distribution of the aerosol droplets and the parenteral administration result in significantly increased bioavailability compared with oral dosage forms.

In preparative chemistry the separation of basic substances such as amines from neutral cannabinoids is not a problem (see under 3.1), so the salts of cannabinoid carboxylic acids with primary, secondary and tertiary amines can also be used outstandingly for the preparation of pure cannabinoids.

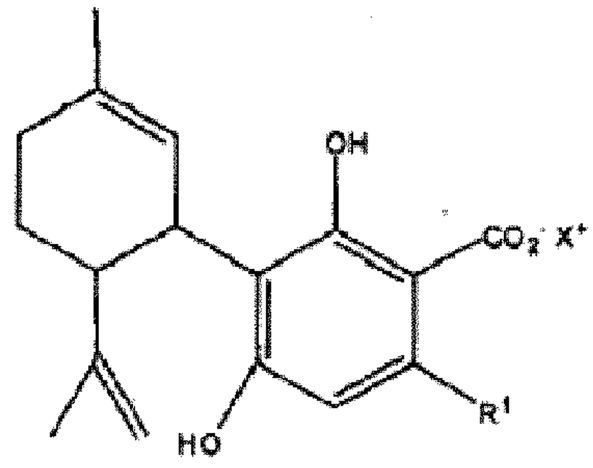
3.2.2 Catalytically assisted decomposition of cannabinoid carboxylic acid salts

The same substances named in 3.1.2 also act catalytically in the decarboxylative decomposition of cannabinoid carboxylic acid salts as in relation to the free cannabinoid carboxylic acids. For more rapid conversion to cannabinoids the salt is moistened with a dilute (e.g. 0.1 %) solution of a transition metal such as for example iron-[III] chloride or silver nitrate. The salt is then dried. Alternatively the salt is thoroughly contacted with a small quantity of transition metals, e.g. 0.1 wt. % steel powder, steel wire or 0.01 % silver powder. Now the salt is heated either dry or together with an inert heat transfer agent, e.g. a high-boiling hydrocarbon. After the salt has been decarboxylated, e.g. through heating for 30 min under inert gas to 180 °C, the procedure described under 3.1 is followed, in order to separate the cannabinoid from the amine.

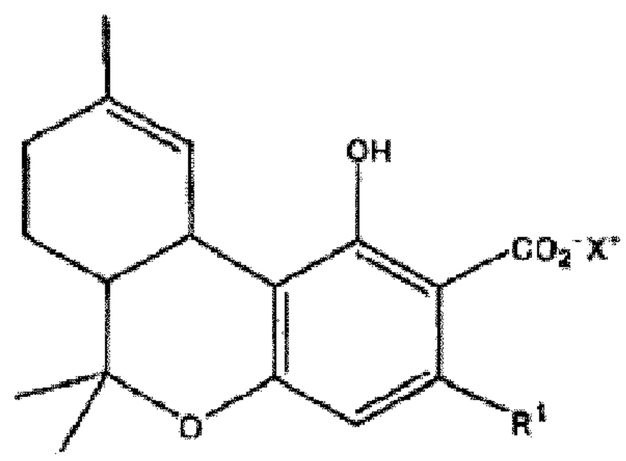
It is clear to the skilled person that the methods described in this application are applicable not only to the explicitly mentioned compounds, but to all homologues, their stereoisomers and to mixtures thereof (e.g. racemates).

Patentkrav

1. Forbindelse valgt fra gruppen omfattende alle stereoisomerer og deres blandinger af forbindelserne med de generelle former (1) - (4)



(1)



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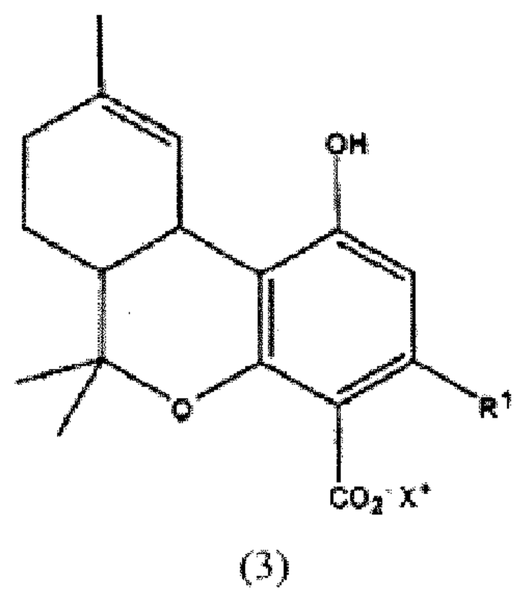
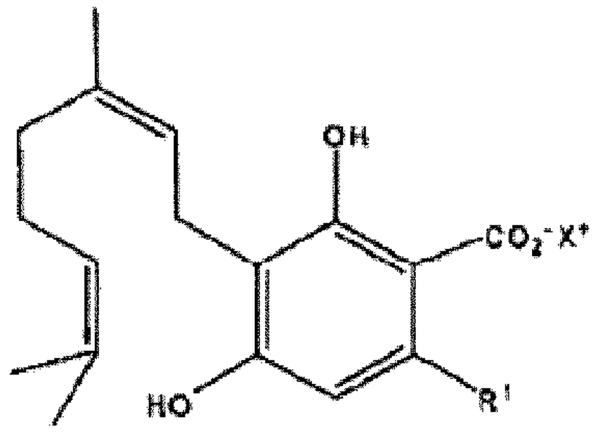


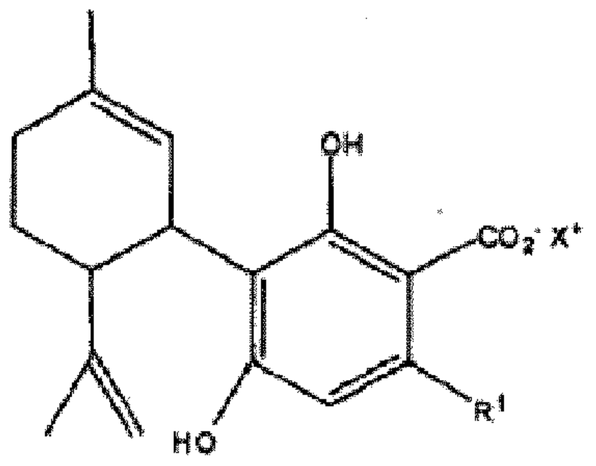
(3)



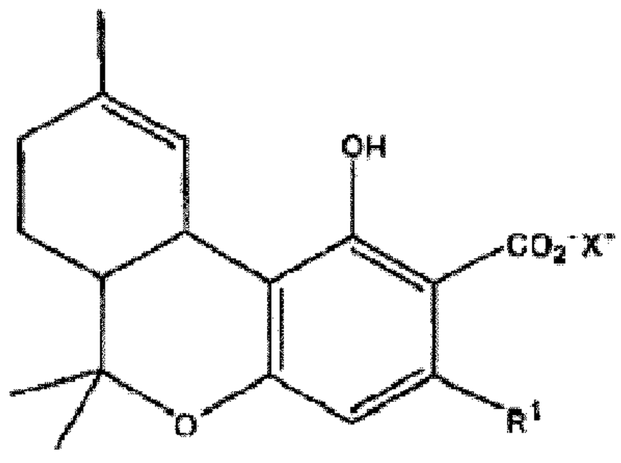
(4)

hvor R^1 er en ligekædet, forgrenet eller cyklisk carbonhydridrest med op til 12 C-atomer, og X^+ er valgt fra gruppen omfattende NH_4^+, primære, sekundære, tertiære eller kvaternære organiske ammoniumioner med op til 48 C-atomer, som kan bære endnu yderligere funktionelle grupper, hydrazinium-ion ($N_2H_5^+$), hydroxylammonium-ion (NH_3OH^+), guanidinium-ion ($CN_3H_6^+$), og organiske derivater af ($N_2H_5^+$), (NH_3OH^+) og ($CN_3H_6^+$), N,N-dicyclohexylamin-H^+ eller N,N-dicyclohexyl-N-ethylamin-H^+ eller hydrogenium-kationen af en aktivt farmaceutisk stof med mindst et basisk nitrogenatom, især morfin, hydromorfon eller methadon eller en isomer deraf.

2. Fremgangsmåde til fremstilling af forbindelser valgt fra gruppen omfattende alle stereoisomerer og deres blandinger af forbindelserne med de generelle formler (1) - (4)



(1)



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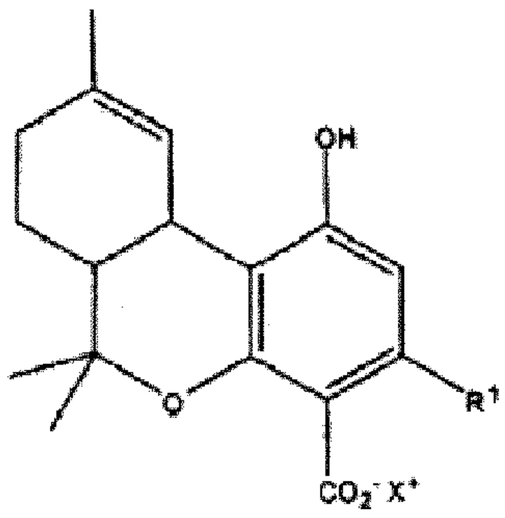
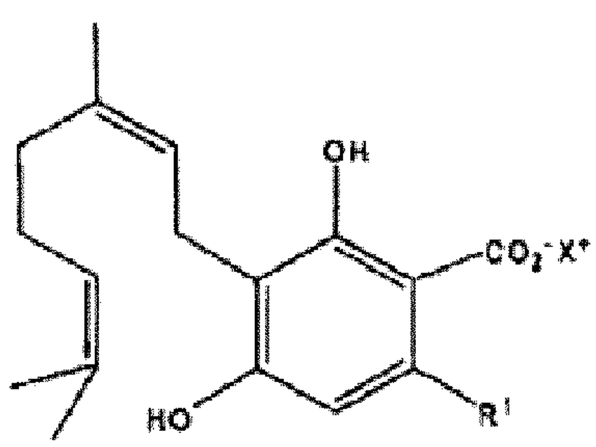


(3)



(4)

hvor R^1 er en ligekædet, forgrenet eller cyklisk carbonhydridrest med op til 12 C-atomer, og

X^+ er valgt fra gruppen omfattende NH_4^+, primære, sekundære, tertiære eller kvaternære organiske ammoniumioner med op til 48 C-atomer, som kan bære endnu yderligere funktionelle grupper, hydrazinium-ion ($N_2H_5^+$), hydroxylammonium-ion (NH_3OH^+), guanidinium-ion ($CN_3H_6^+$), og organiske derivater af ($N_2H_5^+$), (NH_3OH^+) og ($CN_3H_6^+$), N,N-dicyclohexylamin-H^+ eller N,N-dicyclohexyl-N-ethylamin-H^+ eller hydrogenium-kationen af et aktivt farmaceutisk stof med mindst et basisk nitrogenatom, især morfin,

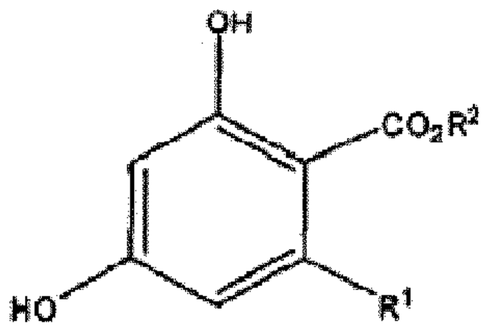
hydromorfon eller methadon eller en isomer deraf, **kendetegnet ved** trinnene

(i) fremstilling af syntetiske cannabinoidcarboxylsyrer i en kemisk reaktion eller ekstraktion af naturlige cannabinoidcarboxylsyrer fra plantemateriale eller cellekulturer af Cannabis sativa; og

(ii) anbringelse af de således fremstillede cannabinoidcarboxylsyrer eller ektrakter rige på cannabinoidcarboxylsyrer i et egnet opløsningsmiddel med en egnet uorganisk base, en egnet organisk base og/eller et egnet uorganisk eller organisk salt, således at de svært opløselige salte af cannabinoidcarboxylsyrerne ifølge krav 1 udfælder.

3. Fremgangsmåde ifølge krav 2, **kendetegnet ved, at** den kemiske reaktion er en carboxylering af naturlige eller syntetiske neutrale cannabinoider.

4. Fremgangsmåde ifølge krav 3, **kendetegnet ved, at** en syrekatalyseret terpenylering af ikke-spaltede eller spaltede alkylresorcylsyrer repræsenterer



(5)

og en efterfølgende forsæbning, hvor R^1 er en ligekædet, forgrenet eller cyklisk carbonhydridrest med op til 12 C-atomer, og R^2 er en ligekædet eller forgrenet alkyl med op til 16 C-atomer, som kan bære yderligere substituenter såsom phenyl, hydroxy, methoxy, ethoxy, halogen eller nitril.

5. Fremgangsmåde ifølge krav 2, **kendetegnet ved, at** ekstraktionen af naturlige cannabinoidcarboxylsyrer udføres ved hjælp af et egnet opløsningsmiddel bestående af gruppen bestående af carbonhydrider med op til 30 C-atomer; petroleumdestillater, især petroleumether, ligroin, kerosen, naphtha; halogenerede carbonhydrider med op til 12 C-atomer, carbondisulfid, estere og ethere med op til 16 C-atomer, alkoholer, ketoner og nitriler med mindst 4 og op til 12 C-atomer, såvel som blandinger af de nævnte opløsningsmidler; vand med basiske tilsætningsstoffer, vand med detergenter, lavere alkoholer med op til 4 C-atomer, acetonitril, propionitril, acetone såvel som blandinger af de nævnte

opløsningsmidler; carbondioxid og flydende svovldioxid, også med tilsætningsstoffer af de førnævnte opløsningsmidler, fortrinsvis i modstrømsprocessen og efterfølgende inddampning, fortrinsvis ved temperaturer under 60°C.

6. Fremgangsmåde ifølge krav 5, **kendetegnet ved, at** til fremstilling af cannabinoidcarboxylsyresaltene er opløsningsmidlet valgt fra gruppen bestående af vand, alkoholer, estere, ethere, ketoner, carbonhydrider, halogenerede carbonhydrider og nitriler med op til 20 C-atomer.

7. Fremgangsmåde ifølge krav 2, **kendetegnet ved, at** de uorganiske eller organiske baser er valgt fra gruppen bestående af primære, sekundære og tertiære organiske aminer med op til 48 C-atomer, som kan bære endnu yderligere funktionelle grupper, især dicyclohexylamin, ammoniak, hydrazin, hydroxylamin, guanidin og organiske derivater af hydrazin, hydroxylamin og guanidin, som kan bære endnu yderligere funktionelle grupper, oxider, alkoxider, hydroxider, carbonater, bicarbonater, caboxylater og andre basiske salte af grundstoffer fra den første, anden og tredje hovedgruppe i det periodiske system såvel som af tin, bly og bismut og overgangsgrundstoffer, såsom især sølv, og ammoniak, enten alene eller i en blanding.

8. Fremgangsmåde ifølge krav 7, **kendetegnet ved, at** den uorganiske base er kompleksbundet for at øge opløseligheden.

9. Fremgangsmåde ifølge krav 2, **kendetegnet ved, at** det organiske salt er valgt fra gruppen bestående af NH_4^+, primære, sekundære, tertiære eller kvaternære ammoniumsalte, især organiske ammoniumsalte med et op til 48 C-atomer, som kan bære endnu yderligere funktionelle grupper, organiske derivater af hydraziniumsalte, hydroxylammoniumsalte og guanidiniumsalte, som kan bære endnu yderligere funktionelle grupper.

10. Fremgangsmåde til fremstilling af rene cannabinoider fra forbindelserne ifølge krav 1 ved tilsætning af egnede vandopløselige syrer i et egnet opløsningsmiddel, fortrinsvis vandopløselig Brønsted-syre med en pKa under 7 og kulsyre.

11. Fremgangsmåde til fremstilling af rene cannabinoider fra forbindelserne ifølge krav 1, **kendetegnet ved, at** forbindelserne nedbrydes termisk.

12. Fremgangsmåde ifølge krav 11, **kendetegnet ved, at** cannabinoidcarboxylsyrer eller deres salte bringes i kontakt med katalytiske stoffer for at fremskynde decarboxylering, især overfladeaktive overgangsmetaller eller opløsninger af overgangsmetaller, såsom jern-(III) chlorid eller sølvnitrat.

13. Anvendelse af forbindelserne ifølge krav 1 som et stof eller deres respektive opløsninger i en indretning, som nedbryder disse termisk eller med katalytisk støtte til neutrale cannabinoider.

14. Anvendelse af de ifølge krav 13 fremstillede neutrale cannabinoider som aerosoler i en indretning til inhalation.

15. Forbindelser ifølge krav 1 til anvendelse i dermatologi.