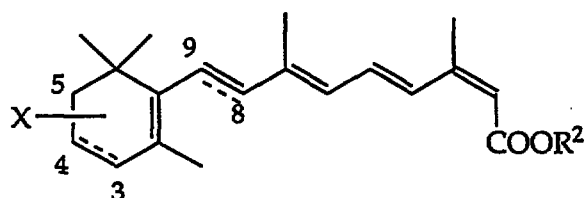



RAN 4051/40

- 5 The present invention is concerned with novel retinoids of the general formula



I

10

wherein

X is oxo or a group OR¹ in the 4- or 5-position;

R¹ is hydrogen, alkyl or acyl; and

R² is hydrogen or alkyl;

- 15 the dotted bonds are optional and a 3,4-double bond can only be present when X is in the 5-position;
 as well as pharmaceutically usable salts of carboxylic acids of formula I.

- 20 Furthermore, the invention is concerned with a process for the manufacture of these retinoids and their salts, pharmaceutical preparations containing these retinoids or their salts as well as the use of these retinoids and their salts as medicaments or for the production of medicaments.

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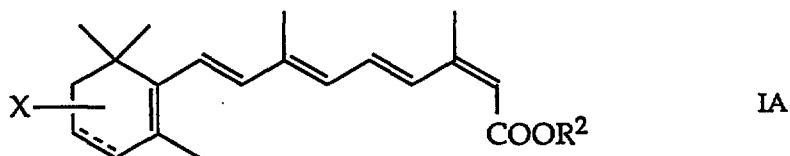
- In the compounds of general formula I alkyl groups are preferably lower alkyl groups (with "lower" denoting groups with 1-7 C atoms), which can be straight-chain or branched, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl,
 30 pentyl, hexyl and heptyl. The term acyl preferably refers to lower alkanoyl groups such as acetyl, propionyl, butyryl and pivaloyl; aromatic acyl groups such as benzoyl and toluy; and araliphatic acyl groups such as phenylacetyl.

Grn/So 12.3.97

REPLACED SHEETS		SG
☒	Description : paged to paged	16
☒	Claim(s) : paged to paged	20
☐	Drawing(s) : paged to paged	
☒	Abstract : paged to paged	21

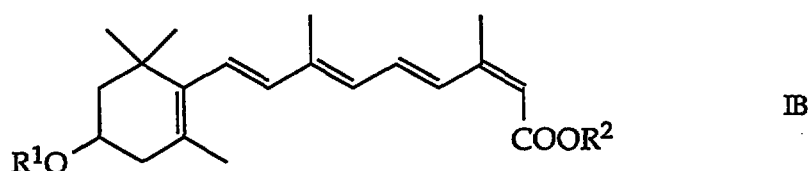
Compounds of formula I in which X is a group OR^1 can be present as R- or S-enantiomers or as racemates.

A preferred group of compounds of formula I comprises
5 compounds of the formula

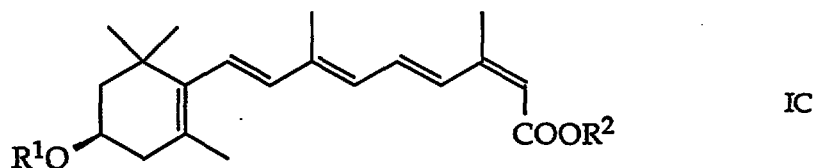


especially those of the formulae

10



and

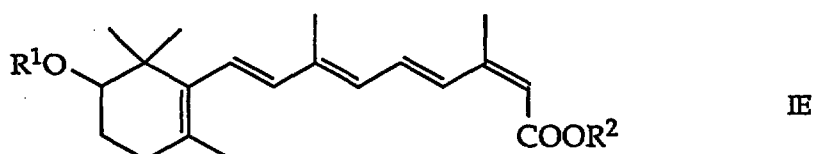
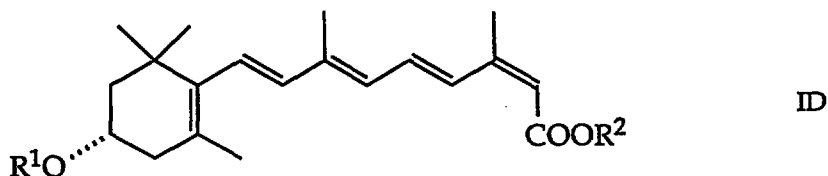


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in which X, R^1 and R^2 have the significance given above.

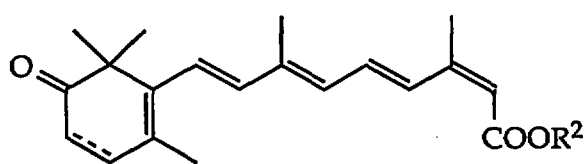
Further sub-groups of compounds of formula I are the
compounds of formulae ID, IE, IF, IG and IH

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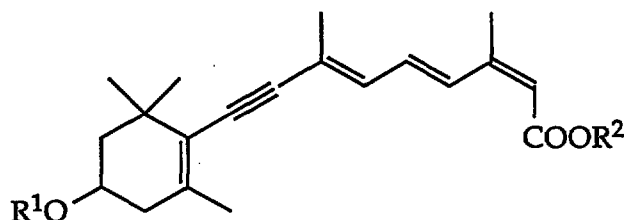


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IF



IG

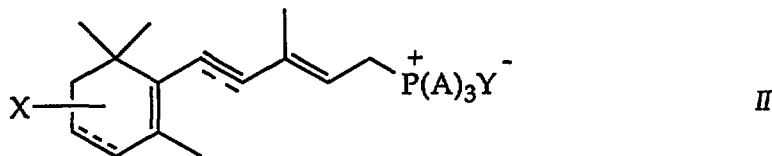
5

Examples of compounds of formula I are:

- (2Z,4E,6E,8E)-(R)-9-(4-Hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid,
- 10 (2Z,4E,6E)-(R)-9-(4-hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6-trien-8-ynoic acid,
- ethyl (2Z,4E,6E,8E)-(R)-9-(4-hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoate,
- (2Z,4E,6E,8E)-9-(5-oxo-2,6,6-trimethyl-cyclohexa-1,3-
- 15 dienyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid,
- (2Z,4E,6E,8E)-(R)-9-(4-acetoxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid,
- (2Z,4E,6E,8E)-(R)-9-(4-methoxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid,
- 20 (2Z,4E,6E,8E)-(RS)-9-(5-hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid,
- (2Z,4E,6E,8E)-(RS)-9-(5-hydroxy-2,6,6-trimethyl-cyclohexa-1,3-dienyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid,
- (2Z,4E,6E,8E)-9-(5-oxo-2,6,6-trimethyl-cyclohex-1-enyl)-
- 25 3,7-dimethyl-nona-2,4,6,8-tetraenoic acid,
- (2Z,4E,6E,8E)-9-(4-oxo-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid,
- (2Z,4E,6E,8E)-(S)-9-(4-hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid and
- 30 (2Z,4E,6E,8E)-(RS)-9-(4-hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid.



The compounds of formula I and their salts can be manufactured in accordance with the invention by reacting a compound of the general formula



5

wherein A is phenyl or substituted phenyl and Y⁻ is an anion, and X and the dotted bonds have the significance given above,

- 10 with 5-hydroxy-4-methyl-5H-furan-2-one in the presence of a base, isomerizing isomers present in the reaction product in which the C=C double bond formed in the reaction has the cis-configuration to the trans isomers and, if desired, subjecting the reaction product of formula I to one or more of the following
- 15 operations:

- a) esterification of a carboxyl or hydroxy group;
- b) etherification of a hydroxy group;
- 20 c) oxidation of a hydroxy group to an oxo group;
- d) reduction of an oxo group to a hydroxy group;
- 25 e) steric inversion of a hydroxy group; and
- f) conversion of a carboxy group into a salt.

The foregoing reactions can be performed according to
30 methods known per se.

The reaction of compound II can be carried out according to the known methods of the Wittig reaction. In this, the reaction partners are reacted with one another in the presence of an acid-binding agent, e.g. in the presence of a strong base, such as KOH in
35 an aqueous solvent; or sodium hydride, K tert.butylate or sodium



ethylate in an anhydrous solvent, such as dimethylformamide or methylene chloride, in a temperature range lying between about -30°C and room temperature. Preferably, compounds of formula II in which X is oxo or hydroxy are used. The Wittig reaction yields
5 a mixture of cis/trans isomers of the C=C double bond formed in the reaction. This mixture of 4E/Z isomers can be isomerized selectively to the 4E-isomers in a manner known per se, e.g. by treatment with Pd catalysts, such as Pd-(II) nitrate.

10 Of the inorganic acid anions Y⁻ the chloride and bromide ions or the hydrosulphate ion are preferred and of the inorganic acid anions the tosyloxy ion is preferred. Group A is preferably phenyl.

15 The esterification of a carboxyl group in a compound of formula I can be carried out e.g. by reaction with an alkyl halide in the presence of a base, such as potassium carbonate, in an organic solvent, such as e.g. ethyl acetate. The esterification of a hydroxy group can be carried out by reaction with an acyl halide
20 in the presence of a base, such as pyridine. A hydroxy group can be oxidized to an oxo group e.g. according to the methods of Swern (dimethyl sulphoxide/oxalyl chloride) or Dess-Martin (periodate). The reduction of an oxo group to a hydroxy group can be carried out with hydride reducing agents such as NaBH₄. The steric
25 configuration of a hydroxy group can be inverted according to the Mitsunobu method (reaction with triphenylphosphine, p-nitrobenzoic acid and diethyl azodicarboxylate and subsequent saponification).

30 Examples of salts into which the carboxylic acids of formula I can be converted are alkali metal salts, such as Na and K salts, alkaline earth metal salts, such as Ca and Mg salts, and ammonium salts, e.g. salts with alkylamines and hydroxyalkylamines or with other organic bases, such as dimethylamine,
35 diethanolamine and piperidine.



The compounds of formula II can be prepared as described in Pure and Appl. Chem. 57, 741 (1985) or the other literature references given therein.

5 The compounds in accordance with the invention can be used for the therapy and prophylaxis of dermatological disorders which are accompanied by epithelial lesions, e.g. acne and psoriasis, as well as malignant and premalignant epithelial lesions, tumours and precancerous changes of the mucous membrane in the mouth,
10 tongue, larynx, oesophagus, bladder, cervix and colon.

The compounds of formula I and their salts can accordingly be used in the form of pharmaceutical preparations.

15 The preparations which are used for systemic administration can be produced e.g. by adding a compound of formula I or a salt thereof as the active ingredient to non-toxic, inert, solid or liquid carriers which are usual in such preparations.

20 The preparations can be administered enterally, parenterally or topically. Preparations in the form of tablets, capsules, dragées, syrups, suspensions, solutions and suppositories are e.g. suitable for enteral administration. Preparations in the form of infusion or injection solutions are
25 suitable for parenteral administration.

For enteral and parenteral administration the compounds of formula I can be administered to adults in amounts of about 10-400 mg/day, preferably 20-200 mg/day.

30 For topical administration the active ingredients are conveniently used in the form of ointments, tinctures, creams, solutions, lotions, sprays, suspensions and the like. Ointments and creams as well as solutions are preferred. These preparations adapted for topical administration can be produced by
35 mixing the process products as active ingredients with non-toxic, inert, solid or liquid carriers which are suitable for topical treatment and which are usual in such preparations.



Conveniently, about 0.1-5%, preferably 0.3-2%, solutions as well as about 0.1-5%, preferably 0.3-2%, ointments or creams are suitable for topical administration.

5

If desired, an antioxidant, e.g. tocopherol, N-methyl- γ -tocopheramine as well as butylated hydroxyanisole or butylated hydroxytoluene, can be admixed with the preparations.

10 The activity of the compounds in accordance with the invention in the treatment of acne can be demonstrated using the test procedures described hereinafter:

1. Inhibition of the proliferation of human sebocytes (in vitro)
15 Literature: Methods in Enzymology 190, 334 (1990), T. Doran and S. Shapiro

2. Changes in the differentiation of pig sebocytes (in vitro),
induction of keratin 7.

20

Cultures of pig sebocytes are prepared from isolated sebum glands of conscious minipigs. They react to treatment with retinoids by expressing keratin 7, which also corresponds to the in vivo situation. Keratin 7 is considered to be a marker for a
25 modified differentiation of sebocytes. The resulting phenotype can no longer produce sebum. The measurement of the keratin 7 induction is based on an ELISA assay using a mouse-monoclonal antikeratin 7-antibody.

30 3. Minipig model (in vivo)

The skin of the minipig has a similar anatomical structure to that of human skin. In particular, the sebum glands resemble those of human acne patients. Under retinoid treatment they
35 show the same histological changes as in human beings. The pigs receive a daily oral dosage of test substance during 8 weeks. A biopsy is taken and investigated histologically every 2 weeks.



In this test the compound prepared in Example 1 shows at a dosage of 10 mg/kg already after 3-4 weeks a clear reduction in sebum glands, which have largely disappeared after 8 weeks. In contrast to isotretinoin, no side effects on skin and mucous
 5 membrane occur at a dosage of 50 mg/kg.

Teratogenic effects belong to the most severe side effects of all retinoids. The compounds claimed herein are significantly less teratogenic than e.g. isotretinoin or tretinoin. The limb bud
 10 cell culture assay (literature: Arch. Toxiol. 60, 403 [1987] A. Kistler) was used to evaluate the teratogenic potential. The correlation between IC₅₀ in this test and the in vivo teratogenicity is very good.

15	<u>Compound of Example</u>	<u>IC₅₀ (nM)</u>
	1	>1000
	3	>1000
	4	>1000
20	Isotretinoin	200
	Tretinoin	80

The invention is illustrated in more detail by the following Examples.

25

Example 1

50 g of [(2E,4E)-(R)-5-(4-hydroxy-2,6,6-trimethyl-1-cyclohexen-1-yl)-3-methyl-2,4-pentadienyl]-triphenylphosphonium chloride were dissolved in 500 ml of isopropanol and
 30 treated with 11 g of 5-hydroxy-4-methyl-5H-furan-2-one. After cooling the reaction mixture to -30°C 120 ml of an aqueous 2N KOH solution were added dropwise and the mixture was stirred at -30°C under argon for a further hour. The reaction mixture was
 35 subsequently poured on to 1.3 l of ice-water, extracted 6 times with 500 ml of a hexane/ethyl acetate mixture (2:1) each time, the aqueous, alkaline solution was acidified by adding ice-cold 3N sulphuric acid while cooling with ice and subsequently extracted



3 times with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried over sodium sulphate and evaporated. The viscous, yellow residue was again dissolved in 800 ml of ethyl acetate, treated with 100 g of silica gel
5 (Merck 0.063-0.2 mm), warmed slightly on a steam bath for 5 minutes while stirring vigorously and, after filtration, concentrated on a rotary evaporator. The thus-obtained yellow, crystalline crude product was treated with 500 ml of acetonitrile and heated to 50°C under argon. A clear, yellow solution
10 was obtained by the portionwise addition of about 700 ml of acetonitrile. After the addition of 1.1 g of triphenylphosphine and 118 ml of a 0.125% solution of palladium(II) nitrate in acetonitrile the reaction mixture was stirred at 50°C for 3 hours. The end product crystallized out upon cooling the
15 reaction solution to -10°C. It was filtered off, washed with hexane and dried at 40°C in a high vacuum. Recrystallization from hexane/ethyl acetate gave 15 g of (2Z,4E,6E,8E)-(R)-9-(4-hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid, m.p. 180-182°C (dec.), $[\alpha]_D^{20} = -49.7$ (c =
20 1, dioxan).

Example 2

3 g of the carboxylic acid obtained according to Example 1
25 were treated in succession with 120 ml of methyl ethyl ketone, 5.2 g of finely ground potassium carbonate and 7.4 g of ethyl iodide and heated at reflux under argon and while stirring vigorously for 2.5 hours. The reaction mixture was poured on to ice/1N hydrochloric acid, extracted with ether, washed with
30 water, dried and evaporated. The oily crude product was filtered over silica gel (eluent hexane/ethyl acetate 2:1) and recrystallized from hexane. There were obtained 2.9 g of ethyl (2Z,4E,6E,8E)-(R)-9-(4-hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoate in yellow crystals, m.p. 93-
35 95°C, $[\alpha]_D^{20} = -45.5$ (c = 1, dioxan).



Example 3

In analogy to Example 1, by reacting 10 g of [(E)-(R)-5-(4-hydroxy-2,6,6-trimethyl-1-cyclohexen-1-yl)-3-methyl-2-penten-4-ynyl]-triphenylphosphonium chloride with 2.3 g of 5-hydroxy-4-methyl-5H-furan-2-one there were obtained, after palladium-catalyzed isomerization of the crude product and recrystallization from hexane/ethyl acetate, 3.1 g of (2Z,4E,6E)-(R)-9-(4-hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6-trien-8-ynoic acid as yellow crystals, m.p. 189-190°C (dec.), $[\alpha]_D^{20} = -87.3$ (c = 1, CHCl₃).

Example 4

9 g of [(2E,4E)-3-methyl-5-(2,6,6-trimethyl-5-oxo-1,3-cyclohexadien-1-yl)-2,4-pentadienyl]triphenylphosphonium bromide and 1.7 g of 5-hydroxy-4-methyl-5H-furan-2-one were suspended in 100 ml of isopropanol. After cooling the reaction mixture to -30°C 20 ml of an aqueous 2N potassium hydroxide solution were added dropwise. After stirring at -30°C for 30 minutes the reaction mixture was poured on to ice-water, extracted 3 times with hexane, the alkaline aqueous phase was acidified with ice-cold 3N sulphuric acid and extracted several times with ethyl acetate. The organic phase was washed with water, dried and evaporated. The brownish, viscous oil was purified by chromatography on silica gel (eluent hexane/ethyl acetate 3:1). The thus-obtained yellow oil (about 4 g) was dissolved in 100 ml of acetonitrile, treated with 150 mg of triphenylphosphine and, after heating to 50°C, 10 ml of a 0.125% palladium(II) nitrate solution in acetonitrile were added dropwise. After heating to 50°C for 2 hours the reaction mixture was cooled to 0°C. After 2 hours the separated crystals were filtered off under suction and recrystallized from hexane/ethyl acetate. There were obtained 1.4 g of (2Z,4E,6E,8E)-9-(5-oxo-2,6,6-trimethyl-cyclohexa-1,3-dienyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid in yellow crystals, m.p. 188°C (dec.).



Example 5

7 g of [(2E,4E)-3-methyl-5-(2,6,6-trimethyl-5-oxo-1-cyclohexen-1-yl)-2,4-pentadienyl]triphenylphosphonium bromide
5 and 1.4 g of 5-hydroxy-4-methyl-5H-furan-2-one were
suspended in 100 ml of isopropanol. After cooling the reaction
mixture to -30°C a solution of 1.76 g of potassium hydroxide in
30 ml of isopropanol was added dropwise thereto. After stirring
10 at -30°C for 40 minutes the reaction mixture was poured on to
200 ml of ice-water, extracted 6 times with a hexane/ethyl
acetate mixture (2:1), the organic phases were washed with
water, the combined, aqueous phases were acidified with 3N
sulphuric acid and extracted several times with ethyl acetate.
The organic phases were washed (H₂O), dried (Na₂SO₄) and
15 evaporated. The oily residue was dissolved in 100 ml of ethyl
acetate, treated with 12 g of silica gel and stirred vigorously at
40°C under argon. After cooling the silica gel was filtered off,
rinsed well with ethyl acetate and the solution was evaporated.
The residue was dissolved in 30 ml of acetonitrile and, after the
20 addition of 256 mg of triphenylphosphine, treated dropwise at
50°C with a solution of 26 mg of palladium nitrate in 5 ml of
acetonitrile. After stirring at 50°C for 1 hour the reaction
mixture was cooled to 0°C and, after 1 hour, the precipitate
which separated was filtered off. After recrystallization twice
25 from hexane/ethyl acetate there were obtained 1.4 g of
(2Z,4E,6E,8E)-3,7-dimethyl-9-(2,6,6-trimethyl-5-oxo-cyclohex-
1-enyl)-nona-2,4,6,8-tetraenoic acid in yellow crystals, m.p.
178-179°C.

30

Example 6

0.5 g of (2Z,4E,6E,8E)-3,7-dimethyl-9-(2,6,6-trimethyl-5-oxo-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoic acid was
dissolved in 25 ml of ethanol while warming slightly and treated
35 with 100 mg of sodium borohydride while cooling with ice. After
stirring at 0°C for 1 hour the reaction mixture was poured on to
ice-water, acidified with 2N hydrochloric acid and extracted with
ethyl acetate. The organic phases were washed (H₂O), dried



(Na₂SO₄) and evaporated. The amorphous residue was filtered over a small column (silica gel, hexane/ethyl acetate = 1:1) and recrystallized from hexane/ethyl acetate. 0.35 g of (2Z,4E,6E,8E)-9-(5-hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid was obtained in yellow crystals, m.p. 152-154°C.

Example 7

2.5 g of the ethyl ester prepared according to Example 2 were dissolved in 35 ml of abs. tetrahydrofuran and treated in succession at 0°C with 3.8 g of triphenylphosphine, 2.4 g of p-nitrobenzoic acid and dropwise with a solution of 2.5 g of diethyl azodicarboxylate in 30 ml of tetrahydrofuran. After stirring at room temperature for 2 hours the mixture was evaporated, the residue was taken up with ether and stored in a refrigerator for 3 hours. The precipitate (triphenylphosphine oxide) which thereby separated was removed, the filtrate was concentrated and the residue was purified by chromatography (silica gel, hexane/ethyl acetate 5%). There was obtained 0.68 g of a yellow oil which was dissolved in 15 ml of ethanol and, after the addition of a solution of 0.78 g of potassium hydroxide in 3 ml of water, 3 ml of ethanol and 3 ml of tetrahydrofuran, stirred at 45°C for 6 hours. The reaction mixture was subsequently poured on to ice-water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The organic phase was washed (H₂O), dried (Na₂SO₄) and evaporated. The crystalline residue was filtered over a small column (silica gel, ethyl acetate) and, after recrystallization from hexane/ethyl acetate, gave 190 mg of (2Z,4E,6E,8E)-(S)-9-(4-hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid in yellow crystals, m.p. 178-180°C, $[\alpha]_D^{20} = +48.2$ (c = 0.66, dioxan).

Example 8

1 g of the carboxylic acid prepared according to Example 4 was suspended in 50 ml of methyl ethyl ketone, treated with 1.5 g of finely ground potassium carbonate and 1.3 ml of ethyl



iodide and heated at reflux for 1 hour. The cooled reaction mixture was poured on to ice-water, neutralized with 1N hydrochloric acid, extracted with ethyl acetate, washed (H_2O), dried (Na_2SO_4) and evaporated. The thus-obtained yellow oil was
5 purified by chromatography (silica gel, hexane/ethyl acetate = 2:1) and gave 1.5 g of the corresponding ethyl ester as a yellow oil.

1.18 g of cerium trichloride $\cdot 7\text{H}_2\text{O}$ were dissolved in 25 ml
10 of methanol and treated in succession with a solution of the above ethyl ester in 5 ml of methanol and 120 mg of sodium borohydride. After the evolution of gas had ceased (about 5 minutes) the mixture was evaporated and the orange residue was purified by chromatography (silica gel, hexane/ethyl acetate
15 = 4:1). 1.04 g of the corresponding hydroxyester were obtained as a yellow oil. This oil was dissolved in 25 ml of ethanol, treated with a solution of 1.6 g of potassium hydroxide in 12 ml of water and stirred at 40°C for 4 hours under argon. The cooled reaction mixture was poured on to ice-water, acidified to pH 3
20 with 1N hydrochloric acid and extracted with ethyl acetate. The organic phase was washed (H_2O), dried (Na_2SO_4) and evaporated and gave 0.95 g of an orange, amorphous residue. Filtration over a small column (silica gel, hexane/ethyl acetate = 1:1) and crystallization from hexane/ethyl acetate gave (2Z,4E,6E,8E)-9-
25 (5-hydroxy-2,6,6-trimethyl-cyclohex-1,3-dienyl)-3,7-dimethylnona-2,4,6,8-tetraenoic acid in yellow-orange crystals, m.p. $108-110^\circ\text{C}$.



Example A

Hard gelatine capsules can be produced as follows:

<u>Ingredient</u>	<u>mg/capsule</u>
1. Spray-dried powder containing 75% compound I	20
2. Sodium dioctylsulphosuccinate	0.2
3. Sodium carboxymethylcellulose	4.8
4. Microcrystalline cellulose	86.0
5. Talc	8.0
6. Magnesium stearate	1.0
Total	120

5

The spray-dried powder, which is based on the active ingredient, gelatine and microcrystalline cellulose and which has an average active ingredient particle size of $<1\mu\text{m}$ (measured by means of autocorrelation spectroscopy), is moistened with an aqueous solution of sodium carboxymethylcellulose and sodium dioctylsulphosuccinate and kneaded. The resulting mass is granulated, dried and sieved, and the granulate obtained is mixed with microcrystalline cellulose, talc and magnesium stearate. The powder is filled into size 0 capsules.

15

Example B

Tablets can be produced as follows:

<u>Ingredient</u>	<u>mg/tablet</u>
1. Compound I as a finely milled powder	20
2. Powd. lactose	100
3. White corn starch	60
4. Povidone K30	8
5. White corn starch	112
6. Talc	16
7. Magnesium stearate	4
Total	320



The finely milled substance is mixed with lactose and a portion of the corn starch. The mixture is moistened with an aqueous solution of Povidone K30 and kneaded, and the resulting mass is granulated, dried and sieved. The granulate is mixed with the remaining corn starch, talc and magnesium stearate and pressed to tablets of suitable size.

Example C

A lotion can be produced as follows:

Ingredient

1. Compound I, finely milled	1.0 g
2. Carbopol 934	0.6 g
3. Sodium hydroxide	q.s. ad pH 6
4. Ethanol, 94%	50.0 g
5. Demineralised water	ad 100.0 g

The active ingredient is incorporated in the 94% ethanol/water mixture with protection from light. Carbopol 934 is stirred in until gelling is complete and the pH value is adjusted with sodium hydroxide.

Example D

A cream can be produced in a manner known per se from the ingredients listed hereinafter:

	<u>Wt. %</u>
Compound of formula I	0.1-5
Cetyl alcohol	5.25-8.75
Arlacel 165 (glyceryl/PEG 100 stearate)	3.75-6.25
Miglyol 818 (caprylic/capric/linoleic acid triglyceride)	11.25-18.75
Sorbitol solution	3.75-6.25



EDTA Na ₂	0.075-0.125
Carbopol 934P (carbomer 934P)	0.15-0.25
Butylated hydroxyanisole	0.0375-0.0625
Methylparaben	0.135-0.225
Propylparaben	0.0375-0.0625
NaOH (10% solution)	0.15-0.25
Water q.s.	100.00

Example E

	<u>Wt.%</u>
Compound of formula I	0.1-5
Pluronic L 101 (poloxamer 331)	10.00
Aerosil 200 (silicon dioxide)	8.00
PCL liquid (fatty acid ester)	15.00
Cetiol V (decyl oleate)	20.00
Neobee oil (medium chain triglyceride)	15.00
Euhanol G (octyldodecanol), q.s.	100.00

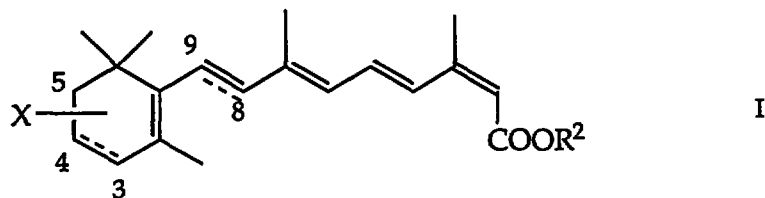
5

The physical properties of the preparation can be altered by varying the ratio between the adjuvants in Examples D and E.



Claims

- ## 1. Compounds of the general formula



wherein

X is oxo or a group OR¹ in the 4- or 5-position;

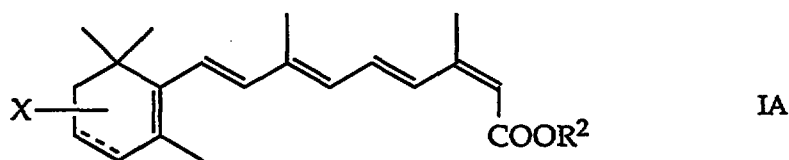
R¹ is hydrogen, alkyl or acyl; and

10 R² is hydrogen or alkyl;

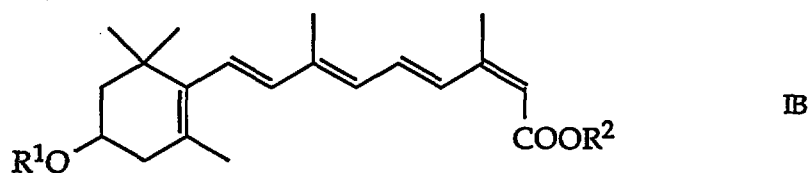
the dotted bonds are optional and a 3,4-double bond can only be present when X is in the 5-position;

as well as pharmaceutically usable salts of carboxylic acids of formula I.

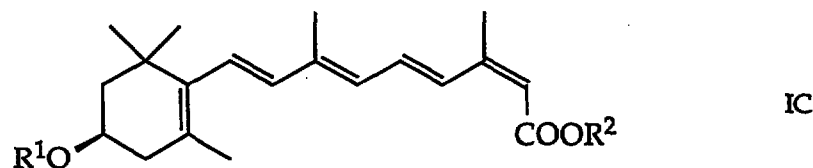
2. Compounds according to claim 1 of the formula



3. Compounds according to claim 1 of the formula



4. Compounds according to claim 1 of the formula





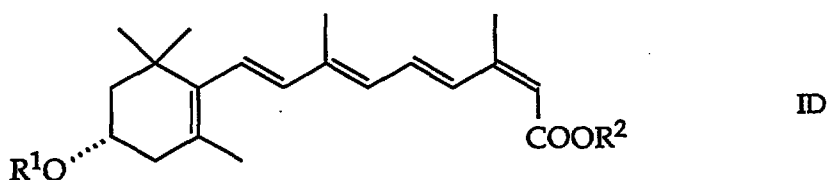
5. (2Z,4E,6E,8E)-(R)-9-(4-Hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid.

6. Ethyl (2Z,4E,6E,8E)-(R)-9-(4-hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoate.

7. (2Z,4E,6E,8E)-(S)-9-(4-Hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid.

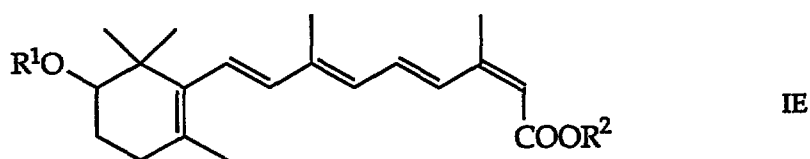
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8. Compounds according to claim 1 of the formula



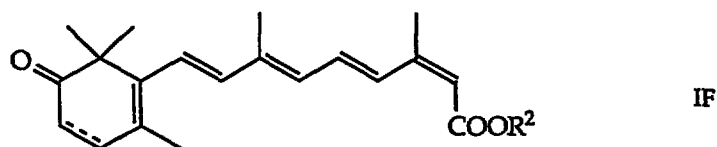
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9. Compounds according to claim 1 of the formula



10. (2Z,4E,6E,8E)-9-(5-Hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid.

11. Compounds according to claim 1 of the formula



25

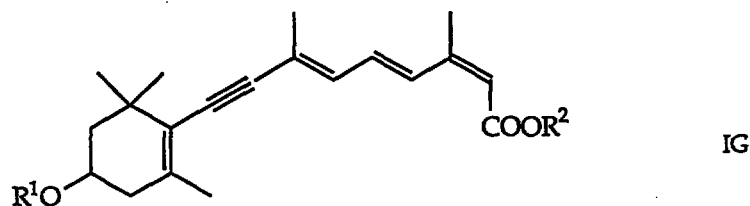
12. (2Z,4E,6E,8E)-9-(5-Oxo-2,6,6-trimethyl-cyclohexa-1,3-dienyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid.

13. (2Z,4E,6E,8E)-3,7-Dimethyl-9-(2,6,6-trimethyl-5-oxo-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoic acid.





14. Compounds according to claim 1 of the formula



5 15. (2Z,4E,6E)-(R)-9-(4-Hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6-trien-8-ynoic acid.

16. The compounds of claims 1-15 for use as medicaments, especially for use in the therapy and prophylaxis of
10 acne, psoriasis, light- and age-damaged skin as well as malignant and premalignant epithelial lesions and inflammations.

17. Pharmaceutical preparations, containing a compound of claims 1-15 and usual pharmaceutical carrier materials.

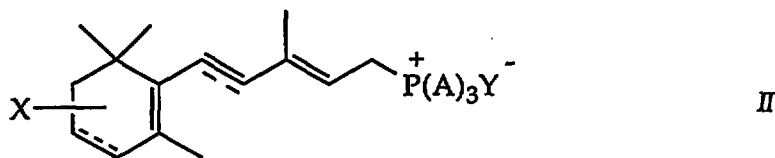
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18. The use of compounds of claims 1-15 for the production of medicaments for the therapy and prophylaxis of acne, psoriasis, light- and age-damaged skin as well as malignant and premalignant epithelial lesions and inflammations.

20

19. A process for the manufacture of the compounds of general formula I and pharmaceutically usable salts thereof, which process comprises reacting a compound of the general formula

25



wherein A is phenyl or substituted phenyl and Y⁻ is an anion, and X and the dotted bonds have the significance given
30 above,

with 5-hydroxy-4-methyl-5H-furan-2-one in the presence of a base, isomerizing isomers present in the reaction product in which the C=C double bond formed in the reaction has the cis-



configuration to the trans isomers and, if desired, subjecting the reaction product of formula I to one or more of the following operations:

- 5 a) esterification of a carboxyl or hydroxy group;
- b) etherification of a hydroxy group;
- c) oxidation of a hydroxy group to an oxo group;
- 10 d) reduction of an oxo group to a hydroxy group;
- e) steric inversion of a hydroxy group; and
- 15 f) conversion of a carboxy group into a salt.

20. The novel compounds, preparations, process and use as described hereinbefore especially with reference to the Examples.

20

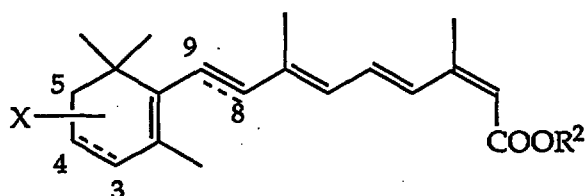
* * *



Abstract

Retinoids of the general formula

5



I

wherein

X is oxo or a group OR¹ in the 4- or 5-position;10 R¹ is hydrogen, alkyl or acyl; andR² is hydrogen or alkyl;

the dotted bonds are optional and a 3,4-double bond can only be present when X is in the 5-position;

15 as well as pharmaceutically usable salts of carboxylic acids of formula I

can be used for the therapy and prophylaxis of dermatological disorders which are accompanied by epithelial lesions, e.g. acne and psoriasis, as well as malignant and premalignant epithelial lesions, tumours and precancerous changes of the mucous membrane in the mouth, tongue, larynx, oesophagus, bladder, cervix and colon.

20

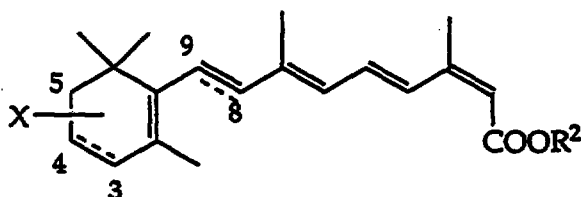


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☒	Claim(s)	: paged 19 to paged 20
☐	Drawing(s)	: paged to paged
☒	Abstract	: paged 21 to paged -
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NOVEL RETINOIDS

- 5 The present invention is concerned with novel retinoids of the general formula



10

wherein

X is oxo or a group OR¹ in the 4- or 5-position;

R¹ is hydrogen, alkyl or acyl; and

R² is hydrogen or alkyl;

- 15 the dotted bonds are optional and a 3,4-double bond can only be present when X is in the 5-position;
as well as pharmaceutically usable salts of carboxylic acids of formula I.

- 20 Furthermore, the invention is concerned with a process for the manufacture of these retinoids and their salts, pharmaceutical preparations containing these retinoids or their salts as well as the use of these retinoids and their salts as medicaments or for the production of medicaments.

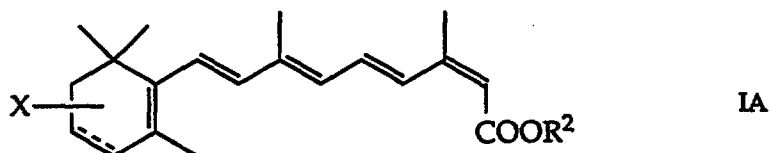
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- In the compounds of general formula I alkyl groups are preferably lower alkyl groups (with "lower" denoting groups with 1-7 C atoms), which can be straight-chain or branched, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, pentyl, hexyl and heptyl. The term acyl preferably refers to lower alkanoyl groups such as acetyl, propionyl, butyryl and pivaloyl; aromatic acyl groups such as benzoyl and toluylyl; and araliphatic acyl groups such as phenylacetyl.

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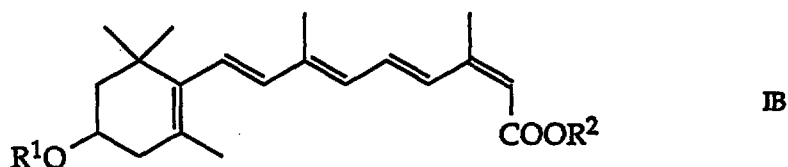
Compounds of formula I in which X is a group OR¹ can be present as R- or S-enantiomers or as racemates.

A preferred group of compounds of formula I comprises
5 compounds of the formula

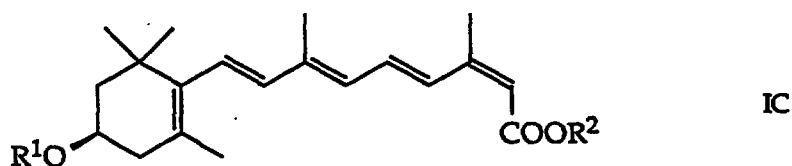


especially those of the formulae

10



and

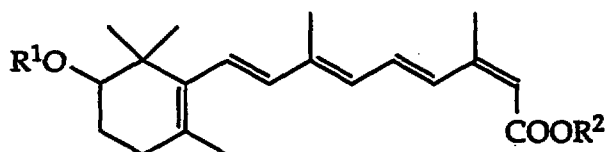
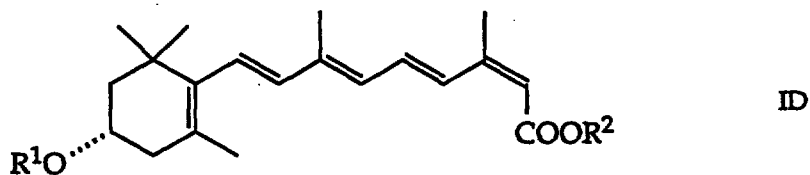


15

in which X, R¹ and R² have the significance given above.

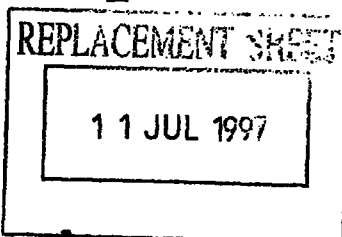
Further sub-groups of compounds of formula I are the
compounds of formulae ID, IE, IF, IG and IH

20



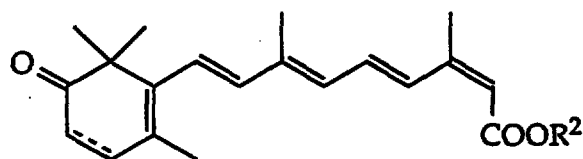
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IE

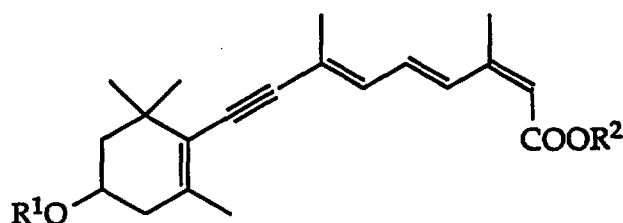


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3



IF



IG

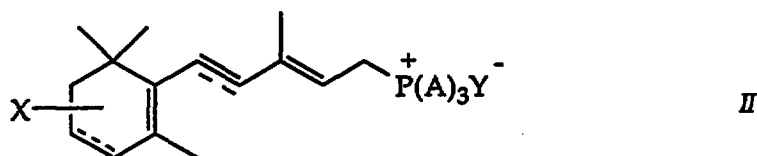
5

Examples of compounds of formula I are:

- (2Z,4E,6E,8E)-(R)-9-(4-Hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid,
- 10 (2Z,4E,6E)-(R)-9-(4-hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6-trien-8-ynoic acid,
- ethyl (2Z,4E,6E,8E)-(R)-9-(4-hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoate,
- (2Z,4E,6E,8E)-9-(5-oxo-2,6,6-trimethyl-cyclohexa-1,3-
- 15 dienyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid,
- (2Z,4E,6E,8E)-(R)-9-(4-acetoxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid,
- (2Z,4E,6E,8E)-(R)-9-(4-methoxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid,
- 20 (2Z,4E,6E,8E)-(RS)-9-(5-hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid,
- (2Z,4E,6E,8E)-(RS)-9-(5-hydroxy-2,6,6-trimethyl-cyclohexa-1,3-dienyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid,
- (2Z,4E,6E,8E)-9-(5-oxo-2,6,6-trimethyl-cyclohex-1-enyl)-
- 25 3,7-dimethyl-nona-2,4,6,8-tetraenoic acid,
- (2Z,4E,6E,8E)-9-(4-oxo-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid,
- (2Z,4E,6E,8E)-(S)-9-(4-hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid and
- 30 (2Z,4E,6E,8E)-(RS)-9-(4-hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid.

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The compounds of formula I and their salts can be manufactured in accordance with the invention by reacting a compound of the general formula



wherein A is phenyl or substituted phenyl and Y⁻ is an anion, and X and the dotted bonds have the significance given above,

- 10 with 5-hydroxy-4-methyl-5H-furan-2-one in the presence of a base, isomerizing isomers present in the reaction product in which the C=C double bond formed in the reaction has the cis-configuration to the trans isomers and, if desired, subjecting the reaction product of formula I to one or more of the following
- 15 operations:

- a) esterification of a carboxyl or hydroxy group;
- b) etherification of a hydroxy group;
- 20 c) oxidation of a hydroxy group to an oxo group;
- d) reduction of an oxo group to a hydroxy group;
- e) steric inversion of a hydroxy group; and
- 25 f) conversion of a carboxy group into a salt.

The foregoing reactions can be performed according to

30 methods known per se.

The reaction of compound II can be carried out according to the known methods of the Wittig reaction. In this, the reaction partners are reacted with one another in the presence of an acid-binding agent, e.g. in the presence of a strong base, such as KOH in

35 an aqueous solvent; or sodium hydride, K tert.butylate or sodium

ethylate in an anhydrous solvent, such as dimethylformamide or methylene chloride, in a temperature range lying between about -30°C and room temperature. Preferably, compounds of formula II in which X is oxo or hydroxy are used. The Wittig reaction yields
5 a mixture of cis/trans isomers of the C=C double bond formed in the reaction. This mixture of 4E/Z isomers can be isomerized selectively to the 4E-isomers in a manner known per se, e.g. by treatment with Pd catalysts, such as Pd-(II) nitrate.

10 Of the inorganic acid anions Y⁻ the chloride and bromide ions or the hydrosulphate ion are preferred and of the inorganic acid anions the tosyloxy ion is preferred. Group A is preferably phenyl.

15 The esterification of a carboxyl group in a compound of formula I can be carried out e.g. by reaction with an alkyl halide in the presence of a base, such as potassium carbonate, in an organic solvent, such as e.g. ethyl acetate. The esterification of a hydroxy group can be carried out by reaction with an acyl halide
20 in the presence of a base, such as pyridine. A hydroxy group can be oxidized to an oxo group e.g. according to the methods of Swern (dimethyl sulphoxide/oxalyl chloride) or Dess-Martin (periodate). The reduction of an oxo group to a hydroxy group can be carried out with hydride reducing agents such as NaBH₄. The steric
25 configuration of a hydroxy group can be inverted according to the Mitsunobu method (reaction with triphenylphosphine, p-nitrobenzoic acid and diethyl azodicarboxylate and subsequent saponification).

30 Examples of salts into which the carboxylic acids of formula I can be converted are alkali metal salts, such as Na and K salts, alkaline earth metal salts, such as Ca and Mg salts, and ammonium salts, e.g. salts with alkylamines and hydroxyalkylamines or with other organic bases, such as dimethylamine,
35 diethanolamine and piperidine.

The compounds of formula II can be prepared as described in Pure and Appl. Chem. 57, 741 (1985) or the other literature references given therein.

5 The compounds in accordance with the invention can be used for the therapy and prophylaxis of dermatological disorders which are accompanied by epithelial lesions, e.g. acne and psoriasis, as well as malignant and premalignant epithelial lesions, tumours and precancerous changes of the mucous membrane in the mouth,
10 tongue, larynx, oesophagus, bladder, cervix and colon.

The compounds of formula I and their salts can accordingly be used in the form of pharmaceutical preparations.

15 The preparations which are used for systemic administration can be produced e.g. by adding a compound of formula I or a salt thereof as the active ingredient to non-toxic, inert, solid or liquid carriers which are usual in such preparations.

20 The preparations can be administered enterally, parenterally or topically. Preparations in the form of tablets, capsules, dragées, syrups, suspensions, solutions and suppositories are e.g. suitable for enteral administration. Preparations in the form of infusion or injection solutions are
25 suitable for parenteral administration.

For enteral and parenteral administration the compounds of formula I can be administered to adults in amounts of about 10-400 mg/day, preferably 20-200 mg/day.

30

For topical administration the active ingredients are conveniently used in the form of ointments, tinctures, creams, solutions, lotions, sprays, suspensions and the like. Ointments and creams as well as solutions are preferred. These preparations adapted for topical administration can be produced by
35 mixing the process products as active ingredients with non-toxic, inert, solid or liquid carriers which are suitable for topical treatment and which are usual in such preparations.

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Conveniently, about 0.1-5%, preferably 0.3-2%, solutions as well as about 0.1-5%, preferably 0.3-2%, ointments or creams are suitable for topical administration.

5

If desired, an antioxidant, e.g. tocopherol, N-methyl- γ -tocopheramine as well as butylated hydroxyanisole or butylated hydroxytoluene, can be admixed with the preparations.

10

The activity of the compounds in accordance with the invention in the treatment of acne can be demonstrated using the test procedures described hereinafter:

1. Inhibition of the proliferation of human sebocytes (in vitro)
15 Literature: Methods in Enzymology 190, 334 (1990), T. Doran and S. Shapiro

2. Changes in the differentiation of pig sebocytes (in vitro), induction of keratin 7.

20

Cultures of pig sebocytes are prepared from isolated sebum glands of conscious minipigs. They react to treatment with retinoids by expressing keratin 7, which also corresponds to the in vivo situation. Keratin 7 is considered to be a marker for a
25 modified differentiation of sebocytes. The resulting phenotype can no longer produce sebum. The measurement of the keratin 7 induction is based on an ELISA assay using a mouse-monoclonal antikeratin 7-antibody.

30 3. Minipig model (in vivo)

The skin of the minipig has a similar anatomical structure to that of human skin. In particular, the sebum glands resemble those of human acne patients. Under retinoid treatment they
35 show the same histological changes as in human beings. The pigs receive a daily oral dosage of test substance during 8 weeks. A biopsy is taken and investigated histologically every 2 weeks.

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In this test the compound prepared in Example 1 shows at a dosage of 10 mg/kg already after 3-4 weeks a clear reduction in sebum glands, which have largely disappeared after 8 weeks. In contrast to isotretinoin, no side effects on skin and mucous
5 membrane occur at a dosage of 50 mg/kg.

Teratogenic effects belong to the most severe side effects of all retinoids. The compounds claimed herein are significantly less teratogenic than e.g. isotretinoin or tretinoin. The limb bud
10 cell culture assay (literature: Arch. Toxiol. 60, 403 [1987] A. Kistler) was used to evaluate the teratogenic potential. The correlation between IC₅₀ in this test and the in vivo teratogenicity is very good.

15	<u>Compound of Example</u>	<u>IC₅₀ (nM)</u>
	1	>1000
	3	>1000
	4	>1000
20	Isotretinoin	200
	Tretinoin	80

The invention is illustrated in more detail by the following Examples.

25

Example 1

50 g of [(2E,4E)-(R)-5-(4-hydroxy-2,6,6-trimethyl-1-cyclohexen-1-yl)-3-methyl-2,4-pentadienyl]-triphenylphosphonium chloride were dissolved in 500 ml of isopropanol and
30 treated with 11 g of 5-hydroxy-4-methyl-5H-furan-2-one. After cooling the reaction mixture to -30°C 120 ml of an aqueous 2N KOH solution were added dropwise and the mixture was stirred at -30°C under argon for a further hour. The reaction mixture was
35 subsequently poured on to 1.3 l of ice-water, extracted 6 times with 500 ml of a hexane/ethyl acetate mixture (2:1) each time, the aqueous, alkaline solution was acidified by adding ice-cold 3N sulphuric acid while cooling with ice and subsequently extracted

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3 times with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried over sodium sulphate and evaporated. The viscous, yellow residue was again dissolved in 800 ml of ethyl acetate, treated with 100 g of silica gel (Merck 0.063-0.2 mm), warmed slightly on a steam bath for 5 minutes while stirring vigorously and, after filtration, concentrated on a rotary evaporator. The thus-obtained yellow, crystalline crude product was treated with 500 ml of acetonitrile and heated to 50°C under argon. A clear, yellow solution was obtained by the portionwise addition of about 700 ml of acetonitrile. After the addition of 1.1 g of triphenylphosphine and 118 ml of a 0.125% solution of palladium(II) nitrate in acetonitrile the reaction mixture was stirred at 50°C for 3 hours. The end product crystallized out upon cooling the reaction solution to -10°C. It was filtered off, washed with hexane and dried at 40°C in a high vacuum. Recrystallization from hexane/ethyl acetate gave 15 g of (2Z,4E,6E,8E)-(R)-9-(4-hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid, m.p. 180-182°C (dec.), $[\alpha]_D^{20} = -49.7$ (c = 1, dioxan).

Example 2

3 g of the carboxylic acid obtained according to Example 1 were treated in succession with 120 ml of methyl ethyl ketone, 5.2 g of finely ground potassium carbonate and 7.4 g of ethyl iodide and heated at reflux under argon and while stirring vigorously for 2.5 hours. The reaction mixture was poured on to ice/1N hydrochloric acid, extracted with ether, washed with water, dried and evaporated. The oily crude product was filtered over silica gel (eluent hexane/ethyl acetate 2:1) and recrystallized from hexane. There were obtained 2.9 g of ethyl (2Z,4E,6E,8E)-(R)-9-(4-hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoate in yellow crystals, m.p. 93-95°C, $[\alpha]_D^{20} = -45.5$ (c = 1, dioxan).

Example 3

In analogy to Example 1, by reacting 10 g of [(E)-(R)-5-(4-hydroxy-2,6,6-trimethyl-1-cyclohexen-1-yl)-3-methyl-2-penten-4-ynyl]-triphenylphosphonium chloride with 2.3 g of 5-hydroxy-4-methyl-5H-furan-2-one there were obtained, after palladium-catalyzed isomerization of the crude product and recrystallization from hexane/ethyl acetate, 3.1 g of (2Z,4E,6E)-(R)-9-(4-hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6-trien-8-ynoic acid as yellow crystals, m.p. 189-190°C (dec.), $[\alpha]_D^{20} = -87.3$ (c = 1, CHCl₃).

Example 4

9 g of [(2E,4E)-3-methyl-5-(2,6,6-trimethyl-5-oxo-1,3-cyclohexadien-1-yl)-2,4-pentadienyl]triphenylphosphonium bromide and 1.7 g of 5-hydroxy-4-methyl-5H-furan-2-one were suspended in 100 ml of isopropanol. After cooling the reaction mixture to -30°C 20 ml of an aqueous 2N potassium hydroxide solution were added dropwise. After stirring at -30°C for 30 minutes the reaction mixture was poured on to ice-water, extracted 3 times with hexane, the alkaline aqueous phase was acidified with ice-cold 3N sulphuric acid and extracted several times with ethyl acetate. The organic phase was washed with water, dried and evaporated. The brownish, viscous oil was purified by chromatography on silica gel (eluent hexane/ethyl acetate 3:1). The thus-obtained yellow oil (about 4 g) was dissolved in 100 ml of acetonitrile, treated with 150 mg of triphenylphosphine and, after heating to 50°C, 10 ml of a 0.125% palladium(II) nitrate solution in acetonitrile were added dropwise. After heating to 50°C for 2 hours the reaction mixture was cooled to 0°C. After 2 hours the separated crystals were filtered off under suction and recrystallized from hexane/ethyl acetate. There were obtained 1.4 g of (2Z,4E,6E,8E)-9-(5-oxo-2,6,6-trimethyl-cyclohexa-1,3-dienyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid in yellow crystals, m.p. 188°C (dec.).

Example 5

7 g of [(2E,4E)-3-methyl-5-(2,6,6-trimethyl-5-oxo-1-cyclohexen-1-yl)-2,4-pentadienyl]triphenylphosphonium bromide
5 and 1.4 g of 5-hydroxy-4-methyl-5H-furan-2-one were
suspended in 100 ml of isopropanol. After cooling the reaction
mixture to -30°C a solution of 1.76 g of potassium hydroxide in
30 ml of isopropanol was added dropwise thereto. After stirring
at -30°C for 40 minutes the reaction mixture was poured on to
10 200 ml of ice-water, extracted 6 times with a hexane/ethyl
acetate mixture (2:1), the organic phases were washed with
water, the combined, aqueous phases were acidified with 3N
sulphuric acid and extracted several times with ethyl acetate.
The organic phases were washed (H₂O), dried (Na₂SO₄) and
15 evaporated. The oily residue was dissolved in 100 ml of ethyl
acetate, treated with 12 g of silica gel and stirred vigorously at
40°C under argon. After cooling the silica gel was filtered off,
rinsed well with ethyl acetate and the solution was evaporated.
The residue was dissolved in 30 ml of acetonitrile and, after the
20 addition of 256 mg of triphenylphosphine, treated dropwise at
50°C with a solution of 26 mg of palladium nitrate in 5 ml of
acetonitrile. After stirring at 50°C for 1 hour the reaction
mixture was cooled to 0°C and, after 1 hour, the precipitate
which separated was filtered off. After recrystallization twice
25 from hexane/ethyl acetate there were obtained 1.4 g of
(2Z,4E,6E,8E)-3,7-dimethyl-9-(2,6,6-trimethyl-5-oxo-cyclohex-
1-enyl)-nona-2,4,6,8-tetraenoic acid in yellow crystals, m.p.
178-179°C.

30

Example 6

0.5 g of (2Z,4E,6E,8E)-3,7-dimethyl-9-(2,6,6-trimethyl-5-oxo-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoic acid was
dissolved in 25 ml of ethanol while warming slightly and treated
35 with 100 mg of sodium borohydride while cooling with ice. After
stirring at 0°C for 1 hour the reaction mixture was poured on to
ice-water, acidified with 2N hydrochloric acid and extracted with
ethyl acetate. The organic phases were washed (H₂O), dried

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(Na₂SO₄) and evaporated. The amorphous residue was filtered over a small column (silica gel, hexane/ethyl acetate = 1:1) and recrystallized from hexane/ethyl acetate. 0.35 g of (2Z,4E,6E,8E)-9-(5-hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-
5 3,7-dimethyl-nona-2,4,6,8-tetraenoic acid was obtained in yellow crystals, m.p. 152-154°C.

Example 7

10 2.5 g of the ethyl ester prepared according to Example 2 were dissolved in 35 ml of abs. tetrahydrofuran and treated in succession at 0°C with 3.8 g of triphenylphosphine, 2.4 g of p-nitrobenzoic acid and dropwise with a solution of 2.5 g of diethyl azodicarboxylate in 30 ml of tetrahydrofuran. After stirring at
15 room temperature for 2 hours the mixture was evaporated, the residue was taken up with ether and stored in a refrigerator for 3 hours. The precipitate (triphenylphosphine oxide) which thereby separated was removed, the filtrate was concentrated and the residue was purified by chromatography (silica gel,
20 hexane/ethyl acetate 5%). There was obtained 0.68 g of a yellow oil which was dissolved in 15 ml of ethanol and, after the addition of a solution of 0.78 g of potassium hydroxide in 3 ml of water, 3 ml of ethanol and 3 ml of tetrahydrofuran, stirred at 45°C for 6 hours. The reaction mixture was subsequently poured
25 on to ice-water, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The organic phase was washed (H₂O), dried (Na₂SO₄) and evaporated. The crystalline residue was filtered over a small column (silica gel, ethyl acetate) and, after recrystallization from hexane/ethyl acetate, gave 190 mg of
30 (2Z,4E,6E,8E)-(S)-9-(4-hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid in yellow crystals, m.p. 178-180°C, $[\alpha]_D^{20} = +48.2$ (c = 0.66, dioxan).

Example 8

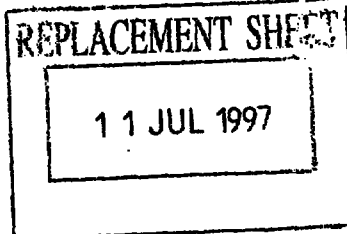
35

1 g of the carboxylic acid prepared according to Example 4 was suspended in 50 ml of methyl ethyl ketone, treated with 1.5 g of finely ground potassium carbonate and 1.3 ml of ethyl

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iodide and heated at reflux for 1 hour. The cooled reaction mixture was poured on to ice-water, neutralized with 1N hydrochloric acid, extracted with ethyl acetate, washed (H_2O), dried (Na_2SO_4) and evaporated. The thus-obtained yellow oil was purified by chromatography (silica gel, hexane/ethyl acetate = 2:1) and gave 1.5 g of the corresponding ethyl ester as a yellow oil.

1.18 g of cerium trichloride•7 H_2O were dissolved in 25 ml of methanol and treated in succession with a solution of the above ethyl ester in 5 ml of methanol and 120 mg of sodium borohydride. After the evolution of gas had ceased (about 5 minutes) the mixture was evaporated and the orange residue was purified by chromatography (silica gel, hexane/ethyl acetate = 4:1). 1.04 g of the corresponding hydroxyester were obtained as a yellow oil. This oil was dissolved in 25 ml of ethanol, treated with a solution of 1.6 g of potassium hydroxide in 12 ml of water and stirred at 40°C for 4 hours under argon. The cooled reaction mixture was poured on to ice-water, acidified to pH 3 with 1N hydrochloric acid and extracted with ethyl acetate. The organic phase was washed (H_2O), dried (Na_2SO_4) and evaporated and gave 0.95 g of an orange, amorphous residue. Filtration over a small column (silica gel, hexane/ethyl acetate = 1:1) and crystallization from hexane/ethyl acetate gave (2Z,4E,6E,8E)-9-(5-hydroxy-2,6,6-trimethyl-cyclohex-1,3-dienyl)-3,7-dimethylnona-2,4,6,8-tetraenoic acid in yellow-orange crystals, m.p. 108-110°C.

Example A

Hard gelatine capsules can be produced as follows:

<u>Ingredient</u>	<u>mg/capsule</u>
1. Spray-dried powder containing 75% compound I	20
2. Sodium dioctylsulphosuccinate	0.2
3. Sodium carboxymethylcellulose	4.8
4. Microcrystalline cellulose	86.0
5. Talc	8.0
6. Magnesium stearate	1.0
Total	120

5

The spray-dried powder, which is based on the active ingredient, gelatine and microcrystalline cellulose and which has an average active ingredient particle size of $<1\mu\text{m}$ (measured by means of autocorrelation spectroscopy), is moistened with an aqueous solution of sodium carboxymethylcellulose and sodium dioctylsulphosuccinate and kneaded. The resulting mass is granulated, dried and sieved, and the granulate obtained is mixed with microcrystalline cellulose, talc and magnesium stearate. The powder is filled into size 0 capsules.

15

Example B

Tablets can be produced as follows:

<u>Ingredient</u>	<u>mg/tablet</u>
1. Compound I as a finely milled powder	20
2. Powd. lactose	100
3. White corn starch	60
4. Povidone K30	8
5. White corn starch	112
6. Talc	16
7. Magnesium stearate	4
Total	320

The finely milled substance is mixed with lactose and a portion of the corn starch. The mixture is moistened with an aqueous solution of Povidone K30 and kneaded, and the resulting mass is granulated, dried and sieved. The granulate is mixed with the remaining corn starch, talc and magnesium stearate and pressed to tablets of suitable size.

Example C

10

A lotion can be produced as follows:

Ingredient

1. Compound I, finely milled	1.0 g
2. Carbopol 934	0.6 g
3. Sodium hydroxide	q.s. ad pH 6
4. Ethanol, 94%	50.0 g
5. Demineralised water	ad 100.0 g

The active ingredient is incorporated in the 94% ethanol/ water mixture with protection from light. Carbopol 934 is stirred in until gelling is complete and the pH value is adjusted with sodium hydroxide.

Example D

20

A cream can be produced in a manner known per se from the ingredients listed hereinafter:

	<u>Wt.%</u>
Compound of formula I	0.1-5
Cetyl alcohol	5.25-8.75
Arlacel 165 (glyceryl/PEG 100 stearate)	3.75-6.25
Miglyol 818 (caprylic/capric/linoleic acid triglyceride)	11.25-18.75
Sorbitol solution	3.75-6.25

EDTA Na ₂	0.075-0.125
Carbopol 934P (carbomer 934P)	0.15-0.25
Butylated hydroxyanisole	0.0375-0.0625
Methylparaben	0.135-0.225
Propylparaben	0.0375-0.0625
NaOH (10% solution)	0.15-0.25
Water q.s.	100.00

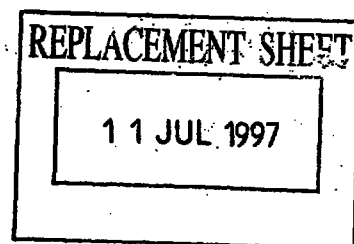
Example E

	<u>Wt. %</u>
Compound of formula I	0.1-5
Pluronic L 101 (poloxamer 331)	10.00
Aerosil 200 (silicon dioxide)	8.00
PCL liquid (fatty acid ester)	15.00
Cetiol V (decyl oleate)	20.00
Neobee oil (medium chain triglyceride)	15.00
Euhanol G (octyldodecanol), q.s.	100.00

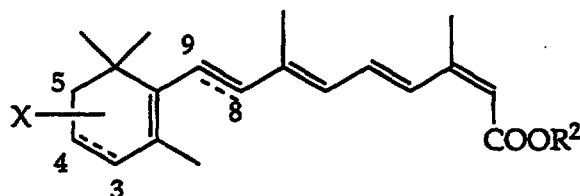
5

The physical properties of the preparation can be altered by varying the ratio between the adjuvants in Examples D and E.

Claims



1. Compounds of the general formula



I

wherein

X is oxo or a group OR^1 in the 4- or 5-position;

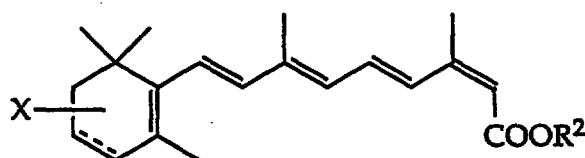
R^1 is hydrogen, alkyl or acyl; and

R^2 is hydrogen or alkyl;

the dotted bonds are optional and a 3,4-double bond can only be present when X is in the 5-position;

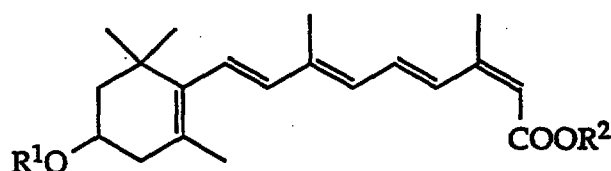
as well as pharmaceutically usable salts of carboxylic acids of formula I.

2. Compounds according to claim 1 of the formula



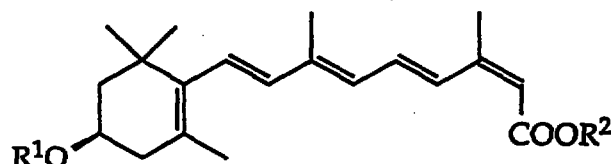
IA

3. Compounds according to claim 1 of the formula



IB

4. Compounds according to claim 1 of the formula



IC

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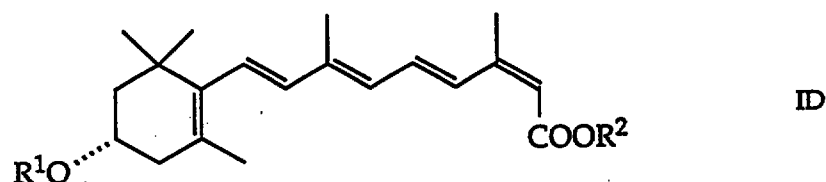


5. (2Z,4E,6E,8E)-(R)-9-(4-Hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid.

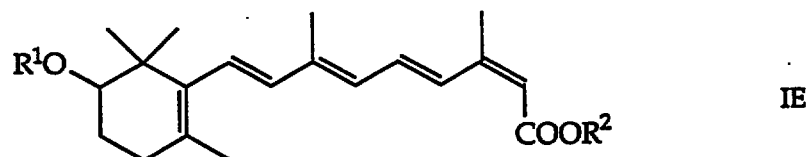
6. Ethyl (2Z,4E,6E,8E)-(R)-9-(4-hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoate.

7. (2Z,4E,6E,8E)-(S)-9-(4-Hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid.

8. Compounds according to claim 1 of the formula

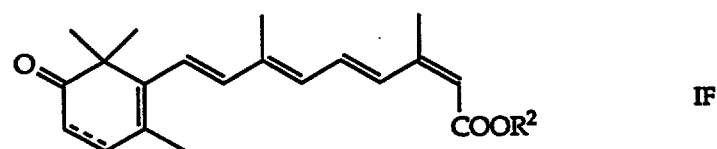


9. Compounds according to claim 1 of the formula



10. (2Z,4E,6E,8E)-9-(5-Hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid.

11. Compounds according to claim 1 of the formula

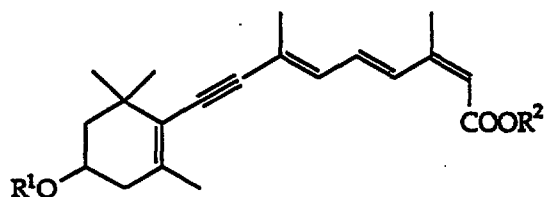


12. (2Z,4E,6E,8E)-9-(5-Oxo-2,6,6-trimethyl-cyclohexa-1,3-dienyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid.

13. (2Z,4E,6E,8E)-3,7-Dimethyl-9-(2,6,6-trimethyl-5-oxo-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoic acid.



14. Compounds according to claim 1 of the formula



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5 15. (2Z,4E,6E)-(R)-9-(4-Hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6-trien-8-ynoic acid.

16. The compounds of claims 1-15 for use as medicaments, especially for use in the therapy and prophylaxis of
10 acne, psoriasis, light- and age-damaged skin as well as malignant and premalignant epithelial lesions and inflammations.

17. Pharmaceutical preparations, containing a compound of claims 1-15 and usual pharmaceutical carrier materials.

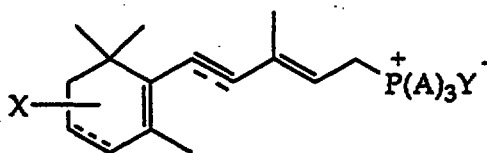
15

18. The use of compounds of claims 1-15 for the production of medicaments for the therapy and prophylaxis of
20 acne, psoriasis, light- and age-damaged skin as well as malignant and premalignant epithelial lesions and inflammations.

20

19. A process for the manufacture of the compounds of general formula I and pharmaceutically usable salts thereof, which process comprises reacting a compound of the general
25 formula

25



II

wherein A is phenyl or substituted phenyl and Y⁻ is an anion, and X and the dotted bonds have the significance given
30 above,

30

with 5-hydroxy-4-methyl-5H-furan-2-one in the presence of a base, isomerizing isomers present in the reaction product in which the C=C double bond formed in the reaction has the cis-

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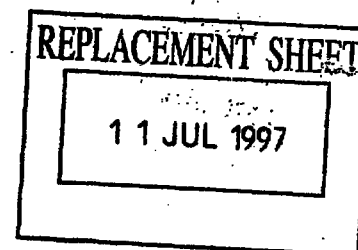


configuration to the trans isomers and, if desired, subjecting the reaction product of formula I to one or more of the following operations:

- 5 a) esterification of a carboxyl or hydroxy group;
- b) etherification of a hydroxy group;
- c) oxidation of a hydroxy group to an oxo group;
- 10 d) reduction of an oxo group to a hydroxy group;
- e) steric inversion of a hydroxy group; and
- 15 f) conversion of a carboxy group into a salt.

20. The novel compounds, preparations, process and use as described hereinbefore especially with reference to the Examples.

20



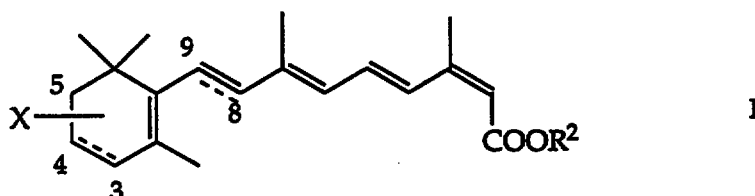
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NOVEL RETINOIDS**Abstract**

Retinoids of the general formula



wherein

X is oxo or a group OR¹ in the 4- or 5-position;

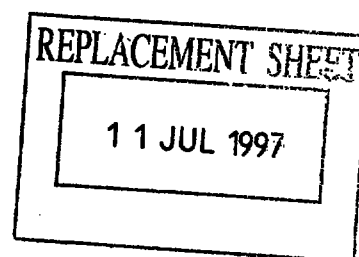
10 R¹ is hydrogen, alkyl or acyl; and

R² is hydrogen or alkyl;

the dotted bonds are optional and a 3,4-double bond can only be present when X is in the 5-position;

as well as pharmaceutically usable salts of carboxylic acids of
15 formula I

can be used for the therapy and prophylaxis of dermatological disorders which are accompanied by epithelial lesions, e.g. acne and psoriasis, as well as malignant and premalignant epithelial
20 lesions, tumours and precancerous changes of the mucous membrane in the mouth, tongue, larynx, oesophagus, bladder, cervix and colon.





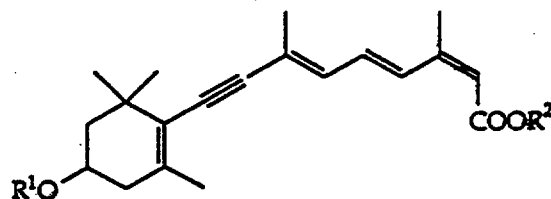
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14. Compounds according to claim 1 of the formula



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5 15. (2Z,4E,6E)-(R)-9-(4-Hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6-trien-8-ynoic acid.

16. The compounds of claims 1-15 for use as medicaments, especially for use in the therapy and prophylaxis of
10 acne, psoriasis, light- and age-damaged skin as well as malignant and premalignant epithelial lesions and inflammations.

17. Pharmaceutical preparations, containing a compound of claims 1-15 and usual pharmaceutical carrier materials.

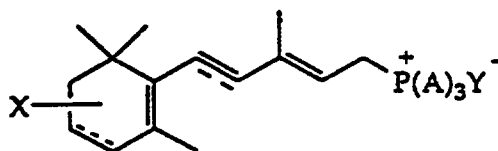
15

18. The use of compounds of claims 1-15 for the production of medicaments for the therapy and prophylaxis of acne, psoriasis, light- and age-damaged skin as well as malignant and premalignant epithelial lesions and inflammations.

20

19. A process for the manufacture of the compounds of general formula I as defined in claim 1 and pharmaceutically usable salts thereof, which process comprises reacting a compound of the general formula

25



II

wherein A is phenyl or substituted phenyl and Y⁻ is an anion, and X and the dotted bonds have the significance given
above,

30

with 5-hydroxy-4-methyl-5H-furan-2-one in the presence of a base, isomerizing isomers present in the reaction product in which the C=C double bond formed in the reaction has the cis-



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configuration to the trans isomers and, if desired, subjecting the reaction product of formula I to one or more of the following operations:

- 5 a) esterification of a carboxyl or hydroxy group;
- b) etherification of a hydroxy group;
- c) oxidation of a hydroxy group to an oxo group;
- 10 d) reduction of an oxo group to a hydroxy group;
- e) steric inversion of a hydroxy group; and
- 15 f) conversion of a carboxy group into a salt.