(CONVENTION. By one or more persons and/or a

60611 COMMONWEALTH (

Patents Act 19

PATENT OFFICE 100 ONE HUNDRED DOLLARS PATENT OFFICE 100 ONE HUNDRED DOLLARS PATENT OFFICE 40 FORTY DOLLARS

LODGED AT SUB-OFFICE 30 DEC 1987 Melbourne

CONVENTION APPLICATION FOR A PATENT

(1) Here insert (in full) Name or Names of Applicant or Applicants, followed by Address (es).

We (1) CENTRE INTERNATIONAL DE RECHERCHES DERMATOLOGIQUES C.I.R.D.

of Sophia Antipolis, F-06560 Valbonne, France

hereby apply for the grant of a Patent for an invention entitled: (2)

(2) Here insert Title of Invention.

EICOSATETRAYNOIC ACID AMIDES AND THEIR APPLICATION IN PHARMACY AND IN COSMETICS

(3) Here insert number(s) of basic application(s)

which is described in the accompanying complete specification. This application is a Convention application and is based on the application numbered (3)

8618419

(4) Here insert Name of basic Country or Countries, and basic date or dates

for a patent or similar protection made in (4) France

on 31st December 1986

LODGED AT SUB-OFFICE 30 DEC 1987 Melbourne

PER STAMP TO VALUE OF $ 2.40 ATTACHED MAIL OFFICER

My/Our address for service is Messrs. Edwd. Waters & Sons, Patent Attorneys, 50 Queen Street, Melbourne, Victoria, Australia.

APPLICATION ACCEPTED AND AMENDMENTS

ALLOWED 7.11.90

DATED this 29th day of December 19 87

(5) Signature (s) of Applicant (s) or Seal of Company and Signatures of its Officers as prescribed by its Articles of Association.

(5) CENTRE INTERNATIONAL DE RECHERCHES DERMATOLOGIQUES C.I.R.D.

by

Ian A. Scott
Registered Patent Attorney

COMMONWEALTH OF AUSTRALIA

Patents Act 1952-1969

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT OR PATENT OF ADDITION

(1) Here insert (in full) Name of Company.

In support of the Convention Application made by(1) CENTRE INTERNATIONAL DE RECHERCHES DERMATOLOGIQUES C.I.R.D.

(hereinafter referred to as the applicant) for a Patent

(2) Here insert title of Invention.

for an invention entitled:(2) EICOSATETRAYNOIC ACID AMIDES AND THEIR APPLICATION IN PHARMACY AND IN COSMETICS

(3) Here insert full Name and Address, of Company official authorized to make declaration.

I,(3) M. SCHAEFER

of Sophia Antipolis, F-06560 Valbonne, France

do solemnly and sincerely declare as follows:

1. I am authorised by the applicant for the patent to make this declaration on its behalf.

2. The basic application as defined by Section 141 of the Act was made in(4) France on the 31st day of December 19 86, by CENTRE INTERNATIONAL DE RECHERCHES DERMATOLOGIQUES C.I.R.D.

(4) Here insert basic Country or Countries followed by date or dates and basic Applicant or Applicants.

XXXXX on the XXXXX day of XXXXXXXXX 19....., by

(5) Here insert (in full) Name and Address of Actual Inventor or Inventors.

3. (5) BRAHAM SHROOT, Villa 35, Hameaux de Val Bosquet, F-06600 Antibes, CHRISTOPHER HENSBY, 89, Chemin d'Andon, Villa Madru, F-06410 Biot, JEAN MAIGNAN, 8, Rue Halevy, F-93290 Tremblay les Gonesses, GERARD LANG, 44, Avenue Lacour F-95210 Saint Gratien, SERGE RESTLE, 140 rue Anatole France F93601 Aulnay-sous-Bois, and MICHEL COLIN, 10 Allee Cecile F-93190 Livry-Gargan, all in France

xxs/are the actual inventors of the invention and the facts upon which the applicant is entitled to make the application are as follow:

The applicant is the assignee of the said actual inventors

4. The basic application referred to in paragraph 2 of this Declaration was the first application made in a Convention country in respect of the invention the subject of the application.

DECLARED at Paris, France

this 2 day of December 19 87

(6) Signature.

(6)

To: THE COMMISSIONER OF PATENTS.

CENTRE INTERNATIONAL DE RECHERCHES DERMATOLOGIQUES SOPHIA ANTIPOLIS 06560 VALBONNE Tél. (93 [illegible]-12-00 R.C. Grasse C 317 099 679 0019

Edwd. Waters & Sons, Melbourne.

(12) PATENT ABRIDGMENT (11) Document No. AU-B-83139/87
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 606111

(54) Title
EICOSATETRAYNOIC ACID AMIDES AND THEIR APPLICATION IN PHARMACY AND IN COSMETICS

International Patent Classification(s)
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(71) Applicant(s)
CENTRE INTERNATIONAL DE RECHERCHES DERMATOLOGIQUES C.I.R.D.

(72) Inventor(s)
BRAHAM SHROOT; CHRISTOPHER HENSBY; JEAN MAIGNAN; GERARD LANG; SERGE RESTLE; MICHEL COLIN

(74) Attorney or Agent
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(56) Prior Art Documents
US 4190669
US 3033884
AU 59786/86 C07C 103/60

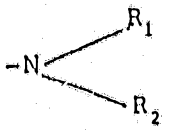
(57) The present invention relates to new compounds consisting of eicosatetraynoic acid amides, as well as to their application, on the one hand as therapeutic agents in the treatment or prophylaxis of allergic conditions and in the treatment of dermatoses and inflammatory conditions, and on the other hand in cosmetic compositions.

CLAIM

1. Compound, characterised in that it corresponds to the formula:

$$C_5H_{11}(C\equiv C-CH_2)_4CH_2CH_2CO\ R \qquad (I)$$

in which R is an amino group of structure



in which R_1 and R_2, which may be identical or different, denote a hydrogen atom or a linear or branched C_1-C_6 lower alkyl radical substituted with at least one hydroxyl group, it being possible for this C_1-C_6

.../2

lower alkyl radical to be interrupted by one or more hetero atoms chosen from oxygen, nitrogen or sulphur, R_1 and R_2 not simultaneously denoting a hydrogen atom and it being possible for R_1 and R_2 to form, with the nitrogen atom to which they are attached, a heterocycle containing one or more nitrogen, oxygen or sulphur atoms as an additional hetero atom, the hetero cycle optionally being substituted with an alkyl or hydroxyalkyl group, and it also being possible for the amino group to be derived from a sugar, and their salts with inorganic or organic acids.

606111

COMMONWEALTH OF AUSTRALIA

Form 10

PATENTS ACT 1952-69

COMPLETE SPECIFICATION

(ORIGINAL)

Class Int. Class

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority :

Related Art :

This document contains the amendments made under Section 49 and is correct for printing.

Name of Applicant : CENTRE INTERNATIONAL DE RECHERCHES DERMATOLOGIQUES C.I.R.D.

Address of Applicant : Sophia Antipolis, F-06560 Valbonne, France

Actual Inventor: ABRAHAM SHROOT, CHRISTOPHER HENSBY, JEAN MAIGNAN, GERARD LANG, SERGE RESTLE ad MICHEL COLIN

Address for Service : EDWD. WATERS & SONS,
50 QUEEN STREET, MELBOURNE, AUSTRALIA, 3000.

Complete Specification for the invention entitled:

EICOSATETRAYNOIC ACID AMIDES AND THEIR APPLICATION IN PHARMACY AND IN COSMETICS

The following statement is a full description of this invention, including the best method of performing it known to us

EICOSATETRAYNOIC ACID AMIDES AND THEIR APPLICATION IN PHARMACY AND IN COSMETICS

The present invention relates to new compounds consisting of eicosatetraynoic acid amides, as well as to their application, on the one hand as therapeutic agents in the treatment or prophylaxis of allergic conditions and in the treatment of dermatoses and inflammatory conditions, and on the other hand in cosmetic compositions.

It is known that a number of substances play an important part in the inflammatory process affecting the skin, such as acne, dermatoses, for example psoriasis, eczema, and the like. These substances, including prostaglandins, hydroxyeicosatetraenoic acids, thromboxanes and leucotrienes, all have a common origin, namely arachidonic acid. (See "VOORHEES-Leuotrienes and Other Lipoxygenase Products in the Pathogenesis and Therapy of Psoriasis and Other Dermatoses" Arch Dermatol, Vol. 119, July 1983, 541-547).

The formation of these substances results chiefly from the release of bound arachidonic acid (bound via an ester bond to lipids present in the epidermis, for example phospholipids), followed by its oxidation by cyclooxygenase and/or lipoxygenases.

For the treatment of skin conditions, either cyclooxygenase inhibitors which prevent prostaglandin formation, such as indomethacin, vitamin E, and the like, or else substances capable of inhibiting lipoxygenases, such as eicosatetraynoic acid, have already been recommended previously.

For the treatment of psoriasis, both 5,8,11,14-eicosatetraynoic acid and 5,8,11-eicosatriynoic acid and their lower alkyl esters have also been recommended (see, in particular, patent US-A-4,190,669).

The Applicant Company has discovered that, surprisingly, particular amides of 5,8,11,14-eicosatetraynoic acid inhibited the enzymatic metabolism of arachidonic acid caused by cyclooxygenase and lipoxygenases. This result is especially unexpected on account of the blocking

of the acid group in the form of the amides defined above.

The Applicant Company has found, moreover, that the bioavailability possessed by these compounds is different from that of the corresponding acids, endowing them with improved therapeutic properties.

The subject of the present invention is hence the new 5,8,11,14-eicosatetraynoic acid amides.

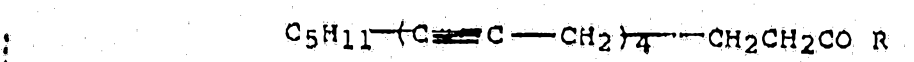
Another subject of the invention consists of the pharmaceutical compositions containing such compounds as active substance.

A subject of the invention also consists of the process for preparing these derivatives.

The subject of the invention is, moreover, the use of these compounds in the cosmetics field, in particular in antiacne, antisun or after-sun compositions, or in the treatment of seborrhoeic dermatitis.

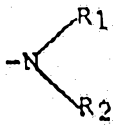
Other subjects of the invention will emerge on reading the description and the examples which follow.

The compounds according to the invention are essentially characterized in that they correspond to the formula:



(I)

in which:

R is an amino group of structure  , in which R_1 and R_2 may be identical or different and correspond to a hydrogen atom or a linear or branched C_1-C_8 lower alkyl radical substituted with at least one hydroxyl group. This C_1-C_8 lower alkyl radical can be interrupted by one or more hetero atoms chosen from oxygen, nitrogen or sulphur;

R_1 and R_2 do not simultaneously denote a hydrogen atom;

R_1 and R_2 can also form, with the nitrogen atom to which they are attached, a heterocycle containing nitrogen, oxygen or sulphur as an additional hetero atom, this heterocycle optionally being substituted with an alkyl or hydroxyalkyl group, the alkyl groups preferably

having 1 to 8 carbon atoms; the amino group can also be derived from a sugar; and their salts with inorganic or organic acids.

The especially preferred compounds according to the invention are the compounds corresponding to the formula (I) in which, when R_1 corresponds to a hydrogen atom and R_2 to an alkyl chain substituted with at least one hydroxyl radical, R_2 denotes:

$-CH_2CH_2OH$ (amide derived from ethanolamine)

$-CH_2CHOHCH_2OH$ (amide derived from 2,3-dihydroxypropylamine)

$-CH_2CHOHCH_3$ (amide derived from 2-hydroxypropylamine);

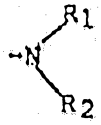
and when the alkyl chain R_2 is interrupted by one or more hetero atoms, the preferred meaning is:

$-CH_2CH_2-O-CH_2CH_2OH$ (amide derived from Diglycolamine).

When R_1 and R_2 are identical, their preferred meaning is:

$-CH_2CH_2OH$ (amide derived from diethanolamine).

When R_1 and R_2 together form a heterocycle, the preferred compounds of the invention are amides derived from morpholine, from piperazine or from 4-(2-hydroxyethyl)piperazine.

When the amino group  is derived from a sugar, the preferred amino sugar is N-methylglucamine.

The especially preferred compounds of the invention are, in particular:

- N-[(2-hydroxyethyl)oxyethyl]-5,8,11,14-eicosatetraynamide
- N,N-bis(2-hydroxyethyl)-5,8,11,14-eicosatetraynamide
- N-(2,3-dihydroxypropyl)-5,8,11,14-eicosatetraynamide
- N-(2-hydroxyethyl)-5,8,11,14-eicosatetraynamide
- N-(2-hydroxypropyl)-5,8,11,14-eicosatetraynamide
- 1-(5,8,11,14-eicosatetraynoyl)-4-(2-hydroxyethyl)piperazine

and their salts with inorganic or organic acids.

The compounds according to the invention are prepared, generally speaking, from 5,8,11,14-eicosatetraynoic acid. This acid is known per se, in particular from

patent US-A-3,033,884.

The subject of the invention is also a new process for preparing this 5,8,11,14-eicosatetraynoic acid, according to the process described in Scheme A below.

This process consists, in a first stage, in treating 1-heptyne (1) with a 1,4-dihalobutyne (2). These two reactants (1) and (2) are known per se. The acetylide of the heptyne (1) is formed, for example, by exchange with an alkyl organomagnesium compound such as, preferably, ethylmagnesium bromide.

This acetylide of the heptyne is reacted with the dihalide (2) which is, preferably, introduced in excess. The 1-halo-2,5-undecadiyne (3) is thereby obtained in good yield.

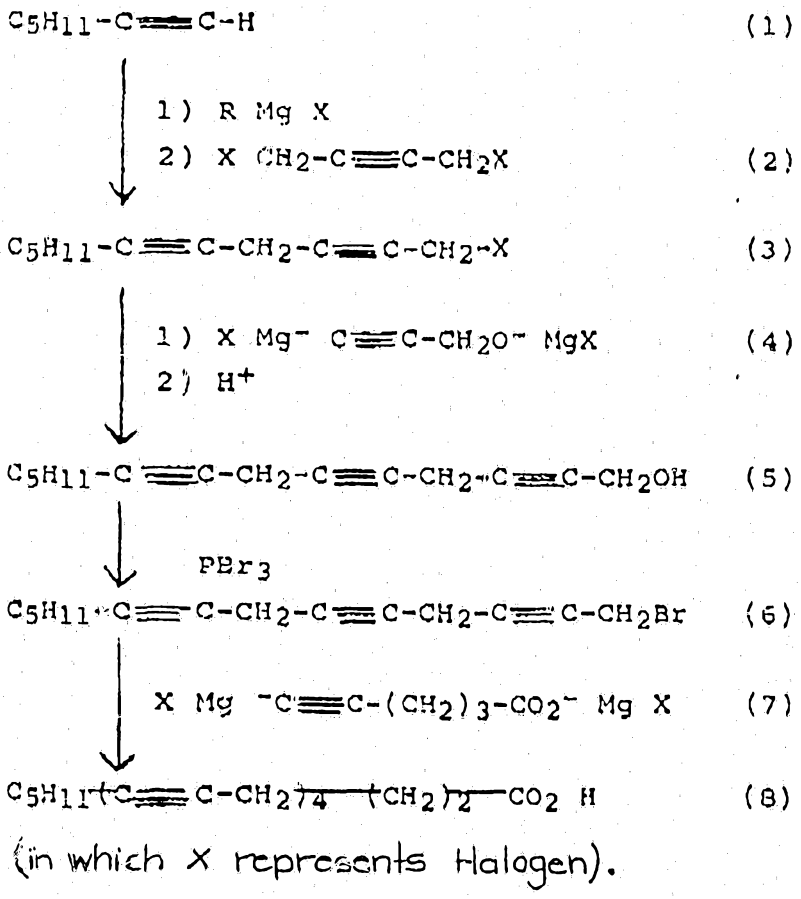
The main advantage of this process is hence to proceed in one stage from a chain containing 7 carbon atoms to a chain containing 11 carbon atoms having a triple bond at the 2-position and the halogen atom at the 1-position.

The syntheses of this halide hitherto described consisted of chain-elongation reactions using propargyl alcohol. The alcohol thereby synthesized was converted to halide by the action of a phosphorus trihalide, which adversely effected the yield of the process.

The transition from the halide having 11 carbon atoms, of formula (3), to 1-hydroxy-2,5,8-tetradecatriyne (5) is accomplished by the action of the dianion of propargyl alcohol (4). This alcohol of formula (5) is converted, in its turn, to 1-bromo-2,5,8-tetradecatriyne of formula (6), by the action of phosphorus tribromide.

These last two stages are described in patent US-A-3,033,884.

5,8,11,14-Eicosatetrynoic acid is obtained by reacting the dianion of 5-hexynecarboxylic acid, according to a known process, with the 1-bromo-2,5,8-tetradecatriyne of formula (6). The synthesis of this 5-hexynecarboxylic acid is described, in particular, in European Patent Application EP-A-86/109,150.



(in which X represents Halogen).

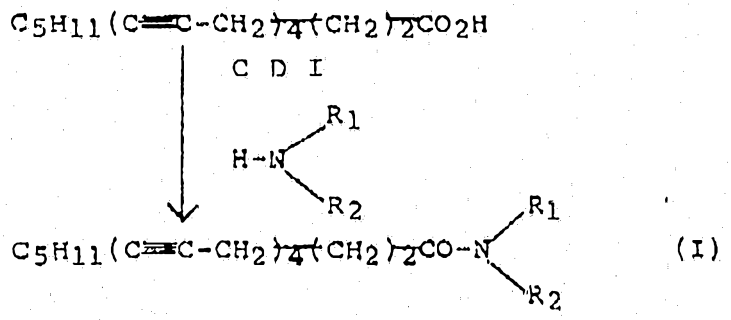
SCHEME A

The amides of formula (I) according to the invention are obtained by reacting an activated form of 5,8,11,14-eicosatetraynoic acid with an amine in an organic solvent.

This activated form of the acid can be either an acid chloride or an anhydride, or alternatively the intermediate formed by adding carbonyldiimidazole (CDI) to a solution of the acid.

This latter reaction is preferably performed in a solvent medium such as dimethylformamide or alternatively in a chlorinated solvent such as dichloromethane or 1,2-dichloroethane. This reaction is illustrated by the

following reaction Scheme B:



SCHEME B

In the formula (I), R_1 and R_2 have the meanings stated above.

The compounds of formula (I) according to the invention have especially notable activity with respect to the inhibition of arachidonic acid metabolism, and particularly as regards the lipoxygenases which are at the origin of the formation of leucotrienes and hydroxylated acids which play an important part in the inflammatory process.

The compounds according to the invention may be administered to man or animals by means of compositions containing, in addition, a pharmaceutically acceptable vehicle or diluent. These compositions can also contain, if so desired, other active substances not having an antagonistic effect on the compounds according to the invention.

The compounds according to the invention may be administered systemically or locally.

For enteral administration, the medicinal products may take the form of tablets, gelatin capsules, dragees, syrups, suspensions, solutions, powders, granules, emulsions, suppositories, and the like. For topical application, the pharmaceutical compositions based on compounds according to the invention take, inter alia,

the form of ointments, tinctures, creams, pomades, powders, patches, impregnated pads, solutions, lotions, gels, sprays, shampoos or suspensions.

These compositions used topically can be presented either in anhydrous form or in aqueous form, according to the clinical indication.

The pharmaceutical compositions according to the invention can also be administered parenterally and, in particular, intravenously, intramuscularly, intraperitoneally, subcutaneously or intradermally.

For parenteral administration, and more especially injections, the active substance is used in a sterile vehicle such as water. The active substance is either suspended or dissolved in the vehicle.

The compounds according to the invention can also be used in cosmetics, in particular in creams, skin lotions such as antisun products, soothing after-sun products, antiseborrhoeic or antiacne products or shampoos.

The medicinal and cosmetic compositions according to the invention can contain inert or pharmacodynamically or cosmetically active additives, and in particular:

hydrating agents such as thiamorpholinone and its derivatives or urea; antiseborrhoeic agents such as S-carboxymethylcysteine, S-benzylcysteamine and their derivatives, bioxolone; antibiotics such as erythromycin and its esters, neomycin, clindamycin and its derivatives or tetracyclines; agents which interfere with keratinisation such as salicylic acid and α-hydroxycarboxylic acids; agents promoting hair regrowth such as minoxidil (2,4-diamino-6-piperidinopyrimidine 3-oxide) and its derivatives, diazoxide and phenytoin; other steroid and non-steroid anti-inflammatory agents; carotenoids and β-carotene in particular; antipsoriatic agents such as anthralin and its derivatives; and phospholipase A_2 inhibitors.

The compositions according to the invention can also contain flavour-improving agents, preservatives, stabilizers, moisture regulators, pH regulators, osmotic

pressure modifying agents, emulsifiers, UV-A and UV-B filters, antioxidants such as α-tocopherol, butylated hydroxyanisole or butylated hydroxytoluene, ascorbic acid, local anaesthetics, buffers, and the like.

The compositions according to the invention can also be packaged in delay or sustained-release forms which are known per se. Lastly, they can be introduced into the aqueous phases of liposomes or niosomes.

The active substance according to the invention is present in the pharmaceutical or cosmetic compositions in proportions of between 0.01 and 10 % by weight based on the total weight of the composition, preferably between 0.1 and 5 % by weight.

In therapeutic application, the treatment is determined by the doctor and can vary according to the age, weight and response of the patient as well as the severity of the symptoms. Dosage is generally between 0.05 and 500 mg/kg/day and preferably 0.5 to 100 mg/kg/day. The treatment period is variable according to the severity of the symptoms, and may extend between 1 and 12 weeks with continuous or discontinuous administration.

In cosmetic application, the compositions according to the invention are chiefly used as antisun products, soothing after-sun products and for the treatment of seborrhoeic dermatitis and/or dermatitis involving acne.

Another subject of the invention consists of the use of the compounds of formula (I) in the preparation of pharmaceutical compositions intended for the treatment or prophylaxis of allergic conditions and in the treatment of acne, dermatoses and inflammatory conditions.

The examples which follow are designed to illustrate the invention without, however, being limiting in nature.

REFERENCE EXAMPLE

Preparation of 5,8,11,14-eicosatetraynoic acid

a) Synthesis of 1-chloro-2,5-undecadiyne

4.17 g (0.17 mol) of magnesium are introduced into a round-bottomed flask equipped with an argon inlet, a condenser and a dropping funnel. The magnesium is covered with THF, a few drops of ethyl bromide are added and the reaction is initiated by heating or by introducing a crystal of iodine. The reaction is maintained at the refluxing point of the THF by the dropwise addition of 14 cm^3 of ethyl bromide dissolved in THF, and the mixture is then heated to 70-80°C until the magnesium has completely disappeared.

15 g of heptyne (0.156 mol) are added, following the evolution of ethane and maintaining the temperature at 70°C. The reaction is highly exothermic. 1.1 g of copper cyanide are introduced and the mixture is heated to 70°C for one hour.

The reaction medium is cooled to 50°C and 43 cm^3 (0.44 mol; 2.8 equivalents) of dichlorobutyne are added rapidly. Since the reaction is highly exothermic, the temperature is maintained below 70°C during the addition by means of a water/ice bath, and the mixture is then heated to 70°C for approximately 2 hours.

Using GC, it is observed that the heptyne has completely disappeared.

The reaction medium is poured into an ice-cold solution (500 cm^3) of ammonium chloride and extracted with ether.

The organic phase is washed, dried over magnesium sulphate and concentrated under reduced pressure.

The expected product is purified by distillation.

The excess dichlorobutyne is removed by distillation at the water pump and the 1-chloro-2,5-undecadiyne is distilled under vacuum using a vane pump.

The expected product distills at 95-105°C at 0.01 mm Hg. It is obtained in a 58 % yield.

The ^1H NMR spectrum (80 MHz) is in agreement with the expected structure.

b) Synthesis of 1-hydroxy-2,5,8-tetradecatriyne

4.8 g of magnesium (0.197 mol) are introduced into a round-bottomed flask equipped with a nitrogen inlet and a dropping funnel. The magnesium is covered with THF, a few drops of ethyl bromide are added and the reaction is initiated by heating or by the addition of an iodine crystal. The reaction is maintained at the refluxing point of the THF by the dropwise addition of 15 cm^3 of ethyl bromide (0.203 mol) dissolved in THF, and the mixture is then heated to 70-80°C until the magnesium has completely disappeared.

The reaction medium is cooled to 0°C and 6.2 cm^3 (0.105 mol) of propargyl alcohol, distilled and stored over a molecular sieve, are added.

The temperature is maintained at 0°C for 30 minutes and the mixture is then heated to 70°C for one hour in order to complete the exchange.

The reaction medium is cooled to 0°C, 0.4 g of copper cyanide is added and the mixture is then heated to 40-45°C for approximately one hour.

A solution of 12 g (0.066 mol) of 1-chloro-2,5-undecadiyne in THF is added and the mixture is brought for approximately 20 hours to the refluxing point of the THF.

The reaction is followed by TLC. At the end of the period of heating, traces of starting 1-chloro-2,5-undecadiyne remain.

The reaction medium is poured into 600 cm^3 of ammonium chloride solution. The product is extracted with ethyl acetate and the organic phases are washed and dried over magnesium sulphate. A brown oil is obtained by concentration under reduced pressure.

This oil is taken up in hot heptane.

By crystallization in the freezer, 6.8 g (yield: 51 %) of a white powder, melting at 26-27°C, are obtained.

The ^1H NMR spectrum is in agreement with the expected structure.

c) Synthesis of 1-bromo-2,5,8-tetradecatriyne

6 g of 1-hydroxy-2,5,8-tetradecatriyne prepared above, dissolved in 30 cm^3 of ethyl ether, are introduced into a round-bottomed flask equipped with an argon inlet. 0.05 cm^3 of pyridine is added and 1 cm^3 of phosphorus tribromide is added dropwise, and the mixture is then brought to reflux for 3 hours.

After it has been verified by TLC that the reaction is complete, the reaction medium is poured into ice-cold water and the expected product extracted with ether. The organic phases are washed with dilute sodium carbonate solution and then with water. They are dried over magnesium sulphate and concentrated under reduced pressure.

8 g of a brown oil are recovered, whose ^1H NMR spectrum (80 MHz) corresponds to the expected structure and which will be used without further treatment for the subsequent reactions.

d) Synthesis of 5,8,11,14-eicosatetraynoic acid

3.8 g (0.156 mol) of magnesium are introduced into a round-bottomed flask equipped with an argon inlet, a condenser and a dropping funnel.

The magnesium is covered with THF and the Grignard reagent formed by adding 13 cm^3 (0.[illegible] mol) of ethyl bromide.

Heating is maintained until the magnesium has completely disappeared.

The reaction medium is cooled to 0°C and 7.7 g of 5-hexynecarboxylic acid, dissolved in THF, are introduced dropwise.

The temperature is allowed to rise to 25°C during 2 hours. 0.6 g of copper cyanide is added, stirring is maintained for 2 hours at room temperature and 8 g (0.03 mol) of 1-bromo-2,5,8-tetradecatriyne obtained above, dissolved in THF, are then added.

The mixture is heated for approximately 20 hours at the refluxing point of the THF. Using TLC, it is observed that the reaction is not proceeding further.

The reaction medium is poured into dilute

hydrochloric acid solution in ice. The product is extracted with ethyl acetate.

The organic phases are washed with sodium hydrogen carbonate solution to remove the excess 5-hexynecarboxylic acid. The organic phase is washed again with water and then dried.

It is concentrated under reduced pressure, and the crude product thereby obtained is then recrystallized in a minimum amount of methanol.

1.5 g of pale cream crystals are recovered, whose melting point is 78-80°C and which appear to be hygroscopic.

The ^1H NMR and IR spectra are in agreement with the expected structure.

Elementary analysis: $C_{20}H_{24}O_2$

	C	H	O
Theoretical value :	81.04	8.16	10.72
Value found :	77.96	8.25	13.73
Theoretical value with 2/3 H_2O :	77.95	8.21	13.85

PREPARATION EXAMPLE 1

Synthesis of N-[(2-hydroxyethyl)oxyethyl]-5,8,11,14-eicosatetraynamide

1.1 g of carbonyldiimidazole are added to a solution, outgassed with argon, of 1.5 g of 5,8,11,14-eicosatetraynoic acid (5 mmol) in 30 cm^3 of anhydrous DMF, and the mixture is heated to 50°C for 1 hour 30 minutes.

The solution is cooled to 0°C and 1.05 g (0.01 mol) of (2-hydroxyethyl)oxyethylamine, dissolved in 10 cm^3 of DMF, is then added.

The mixture is allowed to return to room temperature during 2 hours, and then, after the disappearance of the starting acid has been verified using TLC, the reaction medium is poured into dilute ammonium chloride solution and the product extracted with ethyl acetate. The organic phases are washed with water. They are dried and concentrated under reduced pressure.

The crude reaction product is crystallized in heptane.

By recrystallization in diisopropyl ether, 1.1 g of a white powder is obtained, whose melting point is 68-69°C.

The ^{13}C NMR and IR spectra are in agreement with the expected structure.

Elementary analysis: $C_{24}H_{33}NO_3$

	C	H	N	O
Theoretical value :	75.16	8.67	3.65	12.51
Value found :	74.60	8.73	3.81	13.23

PREPARATION EXAMPLE 2

Synthesis of 1-(5,8,11,14-eicosatetraynoyl)-4-(2-hydroxyethyl)piperazine

1.1 g of carbonyldiimidazole are added to a solution, outgassed with argon, of 1.5 g of 5,8,11,14-eicosatetraynoic acid (5 mmol) in 30 cm^3 of anhydrous DMF, and the mixture is heated to 50°C for 1 hour 30 minutes.

The solution is cooled to 0°C and 1.3 g of (2-hydroxyethyl)piperazine (0.01 mol), dissolved in 10 cm^3 of DMF, is then added.

The mixture is allowed to return to room temperature during 2 hours, and then, after the disappearance of the starting acid has been verified using TLC, the reaction medium is poured into dilute ammonium chloride solution. The product is extracted with diisopropyl ether and the organic phases are washed copiously with water to remove the excess (2-hydroxyethyl)piperazine.
They are dried and concentrated under reduced pressure.

1 g of a brown oil is recovered, whose ^{13}C NMR and IR spectra are in agreement with the expected structure.

Elementary analysis: $C_{26}H_{28}N_2O_2$

	C	H	N	O
Theoretical value :	77.96	7.04	6.99	7.99
Value found :	74.65	8.54	6.74	9.99
Theoretical value with 3/4 H_2O :	75.18	7.20	6.78	10.64

PREPARATION EXAMPLE 3

Synthesis of N-(2-hydroxyethyl)-5,8,11,14-eicosatetraynamide

360 mg of carbonyldiimidazole are added to a solution, outgassed with argon, of 500 mg of 5,8,11,14-eicosatetraynoic acid (1.7 mmol) in 20 cm^3 of anhydrous 1,2-dichloroethane while the solution is maintained at 15°C for approximately 1 hour.

The solution is cooled to 0°C and 200 mg of ethanolamine, dissolved in 1,2-dichloroethane, are then added.

The mixture is left overnight at room temperature, and then, after the disappearance of the starting acid has been verified using TLC, the reaction medium is poured into dilute hydrochloric acid solution.

The product is extracted with dichloromethane and the organic phases are washed copiously with water to remove the excess ethanolamine. They are dried and concentrated under reduced pressure.

250 mg of a white powder are recovered, which is recrystallized in acetonitrile and whose melting point is 93-94°C.

The ^1H NMR (80 MHz) and IR spectra correspond to the expected structure.

PREPARATION EXAMPLE 4

Synthesis of N-(2,3-dihydroxypropyl)-5,8,11,14-eicosatetraynamide

360 mg of carbonyldiimidazole are added to a solution, outgassed with argon, of 500 mg of 5,8,11,14-eicosatetraynoic acid (1.7 mmol) in 20 cm^3 of anhydrous 1,2-dichloroethane while the solution is maintained at 15°C for approximately one hour.

The solution is cooled to 0°C and 310 mg of 3-amino-1,2-propanediol, dissolved in 1,2-dichloroethane, are then added. The mixture is left overnight at room temperature, and then, after the disappearance of the starting acid has been verified using TLC, the reaction medium is poured into dilute hydrochloric acid solution.

The product is extracted with dichloromethane and the organic phases are washed copiously with water to remove the excess 3-amino-1,2-propanediol. They are dried and concentrated under reduced pressure.

200 mg of a white powder are recovered, which is purified by chromatography on silica gel (eluent: chloroform/ethylacetate/methanol) and whose melting point is 95-96°C.

The ^1H NMR (80 MHz) and IR spectra are in agreement with the expected structure.

The examples which follow are designed to illustrate compositions according to the invention.

EXAMPLE 1

The following composition is prepared:

- N-(2-hydroxyethyl)-5,8,11,14-eicosatetraynamide 5.0 g
- Micronized polyethylene 10.0 g
- Isopropyl myristate qs 100.0 g

This composition takes the form of a hydrophobic ointment intended for topical application. Good results are also obtained by replacing the N-(2-hydroxyethyl)-5,8,11,14-eicosatetraynamide in this ointment by N-(2,3-dihydroxypropyl)-5,8,11,14-eicosatetraynamide or by N-[(2-hydroxyethyl)oxyethyl]-5,8,11,14-eicosatetraynamide.

EXAMPLE 2

The following composition is prepared:

- N-(2,3-dihydroxypropyl)-5,8,11,14-eicosatetraynamide 1.0 g
- Triglycerides of capric, caprylic and stearic acids 40.0 g
- Triglycerides of capric and caprylic acids 30.0 g
- Vaseline 20.0 g
- Liquid paraffin qs 100.0 g

This composition takes the form of a hydrophobic ointment intended for topical application.

EXAMPLE 3

The following composition is prepared:

- 1-(5,8,11,14-Eicosatetraynoyl)-4-(2-hydroxyethyl)piperazine 0.5 g

- Cetyl alcohol 6.4 g
- Cetyl alcohol oxyethylenated with 20 mol of ethylene oxide 2.1 g
- Glycerol monostearate 2.0 g
- Triglycerides of capric and caprylic acids 15.0 g
- Propylene glycol 10.0 g
- Water qs 100.0 g

This composition takes the form of a cream intended for topical application.

EXAMPLE 4

The following lotion is prepared:

- N-(2,3-dihydroxypropyl)-5,8,11,14-eicosatetraynamide 0.1 g
- Ethanol 50.0 g
- Propylene glycol qs 100.0 g

This lotion is used for topical application.

The compositions of Examples 1 to 4 above are all manufactured and stored in an inert atmosphere and shielded from the light.

EXAMPLE 5

The following composition is prepared:

- N-(2,3-dihydroxypropyl)-5,8,11,14-eicosatetraynamide 0.01 g
- Absolute ethanol 1.0 ml
- Flavouring qs, preservative qs,
- Glycerol qs 5.0 ml

which is introduced into a 5-ml brown glass ampoule and intended for oral use in the form of a solution to be taken by mouth.

EXAMPLE 6

A 350-mg gelatin capsule is prepared containing a powder having the following composition:

- N-[(2-hydroxyethyl)oxyethyl]-5,8,11,14-eicosatetraynamide 0.025 g
- Microcrystalline cellulose 0.020 g
- Maize starch 0.100 g
- Colloidal silica 0.020 g
- Magnesium stearate 0.185 g

EXAMPLE 7

Granules having the following composition are prepared:

- 1-(5,8,11,14-Eicosatetraynoyl)-4-(2-hydroxyethyl)piperazine	0.500 g
- Methyl cellulose	0.020 g
- Purified water	0.400 g
- Sucrose	1.480 g

The paste obtained by mixing the four constituents is granulated by the wet method and dried.

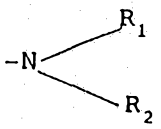
The granules are presented in 2-g sachets, the recommended dosage being four sachets per day.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Compound, characterised in that it corresponds to the formula:

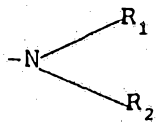
$$C_5H_{11}(C\equiv C-CH_2)_4CH_2CH_2CO\ R \qquad (I)$$

in which R is an amino group of structure



in which R_1 and R_2, which may be identical or different, denote a hydrogen atom or a linear or branched C_1-C_8 lower alkyl radical substituted with at least one hydroxyl group, it being possible for this C_1-C_8 lower alkyl radical to be interrupted by one or more hetero atoms chosen from oxygen, nitrogen or sulphur, R_1 and R_2 not simultaneously denoting a hydrogen atom and it being possible for R_1 and R_2 to form, with the nitrogen atom to which they are attached, a heterocycle containing one or more nitrogen, oxygen or sulphur atoms as an additional hetero atom, the hetero cycle optionally being substituted with an alkyl or hydroxyalkyl group, and it also being possible for the amino group to be derived from a sugar, and their salts with inorganic or organic acids.

2. Compound according to Claim 1, characterised in that it corresponds to the formula (I) in which R denotes the group:



in which R_1 denotes hydrogen and R_2 one of the following groups:

$-CH_2CH_2-OCH_2CH_2OH$, $-CH_2CH_2OH$, $-CH_2-CHOHCH_3$ or $-CH_2CHOHCH_2OH$.

3. Compound according to Claim 1, characterised in that R_1 and R_2 form a ring derived from morpholine, from piperazine and from 4-(2-hydroxyethyl) piperazine.

4. Compound according to Claim 2, characterised in that it is N-[(2-hydroxyethyl)oxyethyl]-5,8,11,14-eicosatetraynamide.

5. Compound according to Claim 2, characterised in that it is N-(2-hydroxyethyl)-5,8,11,14-eicosatetraynamide.

6. Compound according to Claim 2, characterised in that it is N-(2,3-dihydroxypropyl)-5,8,11,14-eicosatetraynamide.

7. Compound according to Claim 2, characterised in that it is 1-(5,8,11,14-eicosatetraynoyl)-4-(2-hydroxyethyl) piperazine.

~~8. Process for preparing eicosatetraynoic acid,~~ characterised in that 1-heptyne, corresponding to the formula:

$$C_5H_{11}-C\equiv C-H \qquad (1)$$

is treated with a strong base to form the corresponding acetylide, which is reacted with the 1,4-dihalo-2-butyne of formula:

$$XCH_2-C\equiv C-CH_2X \qquad (2)$$

to obtain the 1-halo-2, 5-undecadiyne of formula:

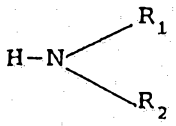
$$C_5H_{11}-C\equiv C-CH_2-C\equiv C-CH_2X \qquad (3)$$

which is reacted with the dianion of propargyl alcohol, the resulting product being brominated by means of phosphorus tribromide to obtain 1-bromo-2,5,8-tetradecatriyne, of formula:

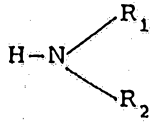
$$C_5H_{11}-C\equiv C-CH_2-C\equiv C-CH_2-C\equiv C-CH_2-Br \qquad (6)$$

which is reacted with the dianion of 5-hexynecarboxylic acid.

8. Process for preparing the compounds according to any one of Claims 1 to 7, characterised in that 5,8,11,14-eicosatetraynoic acid is converted to the corresponding acid chloride or acid anhydride, which is reacted in the presence of a tertiary amine with an amine of formula:



in which R_1 and R_2 have the meaning stated in Calim 1, or in that 5,8,11,14-eicosatetraynoic acid is reacted with carbonyldiimidazole in the presence of a solvent and in that an excess of amine of formula:



in which R_1 and R_2 have the meanings stated in Claim 1, is then added.

9. Preparation process according to Claim 8, characterised in that 5,8,11,14-eicosatetraynoic acid, prepared according to Claim 8, is used.

10. Medicinal product, characterised in that it contains a compound as defined in any one of Claims 1 to 7.

11. Pharmaceutical composition intended for systemic or local administration, characterised in that it contains, in the presence of a vehicle or of a pharmaceutically acceptable diluent, at least one compound as defined in any one of Claims 1 to 7.

12. Pharmaceutical composition intended for topical administration, which takes the form of creams, tinctures, ointments, pomades, powders, patches, impregnated pads, solutions, gels, lotions, sprays or suspension, characterised in that it contains at least one compound as defined in any one of Claims 1 to 7.

13. Pharmaceutical composition which takes the form of a composition intended for parenteral administration intravenously, intraperitoneally, intramuscularly, subcutaneously or intradermally, characterised in that it contains a compound as defined in any one of Claims 1 to 7, in a pharmaceuticcally acceptable diluent.

14. Pharmaceutical composition intended for enteral administration, which takes the form of tablets, gelatin capsules, dragees, syrups, suspensions, solutions, powders, granules or emulsions, characterised in that it contains a compound as defined in any one of Claims 1 to 7.

15. Pharmaceutical composition according to any one of Claims 11 to 13, characterised in that it contains the active compound of formula (I) in the proportions of 0,01 to 10% by weight based on the total weight of the composition, and preferably between 0,1 and 5% by weight.

16. Use of a compound as defined in any one of Claims 1 to 7 for preparing a medicinal product intended for the treatment andd prophylaxis of allergic conditions and for the treatment of dermatoses and inflammatory conditions such as psoriasis, eczema and acne.

17. Use according to Claim 16 of a compound defined in any one of Claims 1 to 7 for preparing a medicinal product designed for the treatment and prophpylaxis of allergic conditions and for the treatment of dermatoses and inflammatory conditions such as psoriasis, eczema and acne, at doses of 0.05 to 100 mg/kg/day, and preferably 0.5 to 50 mg/kg/day.

18. Cosmetic composition, characterised in that it contains at least one compound as defined in any one of Claims 1 to 7, in a proportion of between 0.01 and 10% by weight, and preferably between 0.1 and 5% by weight, based on the total weight of the composition, in the presence of a cosmetically acceptable vehicle.

19. Application of a compound as defined in any one of Claims 1 to 7 as a cosmetic product.

DATED this 22nd day of January, 1988.

CENTRE INTERNATIONAL DE RECHERCHES DERMATOLOGIIQUES

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