57350/86

APPLICATION ACCEPTED AND AMENDMENTS

AS AMENDED 20-4-90

FORM 1

599029

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

APPLICATION FOR A PATENT

We TAKEDA CHEMICAL INDUSTRIES LTD
of 27, Doshomachi 2-chome, Higashi-ku, OSAKA 541 JAPAN
hereby apply for the grant of a patent for an invention entitled:

"ASCORBIC ACID DERIVATIVES, PRODUCTION AND USE THEREOF"

which is described in the accompanying complete specification.

This application is a Convention Application and is based on the application(s) numbered: PCT/JP85/272 and PCT/JP85/340
for a patent or similar protection made in Monaco
on 17 May 1985 and 18 June 1985 respectively

Our address for service is C/- GRIFFITH HACK & CO.
71 YORK STREET
SYDNEY NSW 2000
AUSTRALIA

DATED this 11th day of April 1989

TAKEDA CHEMICAL INDUSTRIES LTD
By their Patent Attorneys

GRIFFITH HACK & CO.

TO: THE COMMISSIONER OF PATENTS,
COMMONWEALTH OF AUSTRALIA.

9699A/sy

FORM 8

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

DECLARATION IN SUPPORT OF AN APPLICATION FOR A PATENT

In support of an application made by: TAKEDA CHEMICAL INDUSTRIES, LTD.

for a patent for an invention entitled: "ASCORBIC ACID DERIVATIVES, PRODUCTION AND USE THEREOF"

I, Hiroshi Iwata, Director, General Manager, Patent & Licensing Dept.
of 105, 4-4, Terahata 2-chome, Kawanishi, Hyogo, Japan

do solemnly and sincerely declare as follows:

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

2. The name and address of each actual inventor of the invention is as follows:

SHINJI TERAO of 26-3, Shinsenri-minamimachi 2-chome, Toyonaka-shi, Osaka 565, Japan and MINORU HIRATA of 26-13, Fushiodai 1-chome, Ikeda-shi, Osaka 563 Japan

and the fact(s) upon which the applicant is entitled to make this application are as follows:

The applicant is the assignee of the said invention from the inventor(s)

3. The basic applications as defined by Section 141 of the Act were made as follows:

Country MONACO on 17th May 1985
in the name(s) TAKEDA CHEMICAL INDUSTRIES, LTD.

Country MONACO on 18th June 1985
in the name(s) TAKEDA CHEMICAL INDUSTRIES, LTD.

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

Declared at Osaka this 9th day of February 1989.
Takeda Chemical Industries, Ltd.

Signed: Hiroshi Iwata

Hiroshi Iwata, Director

Position: General Manager, Patent & Licensing Dept
~~Authorised Signing Officer~~

GRIFFITH HACK & CO.
G.P.O. BOX 4164
SYDNEY N.S.W 2001
AUSTRALIA

3763A/elm

(12) PATENT ABRIDGMENT (11) Document No. AU-B-57350/86
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 599029

(54) Title
ASCORBIC ACID DERIVATIVES

International Patent Classification(s)
(51)[4] C07D 307/62 C07D 405/12 C07D 407/04 A61K 031/375

(21) Application No. : 57350/86 (22) Application Date : 12.05.86

(30) Priority Data

(31) Number	(32) Date	(33) Country
JP 8500272	17.05.85	WO WORLD INTELLECTUAL PROPERTY ORGANIS
		WO WORLD INTELLECTUAL PROPERTY ORGANIS
JP 8500340	18.06.85	WO WORLD INTELLECTUAL PROPERTY ORGANIS
		WO WORLD INTELLECTUAL PROPERTY ORGANIS

(43) Publication Date : 20.11.86

(44) Publication Date of Accepted Application : 12.07.90

(71) Applicant(s)
TAKEDA CHEMICAL INDUSTRIES LTD

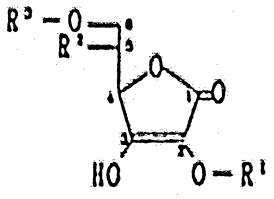
(72) Inventor(s)
SHINJI TERAO; MINORU HIRATA

(74) Attorney or Agent
GRIFFITH HACK & CO. SYDNEY

(56) Prior Art Documents
DE 1468406
DE 1518988
GB 2109382

(57) Claim

1. A method of treating prophylaxis or for improving disorders in functions of the circulatory systems of mammals using a pharmaceutical composition containing an effective amount of an ascorbic acid derivative of the formula:

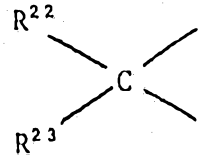


[I]

wherein R^1 is straight-chain or branched alkyl having 1 to 22 carbon atoms which may be substituted with a member selected from a group consisting of hydroxyl, carboxyl, aminocarbonyl, vinyl, ethynyl, cycloalkyl, aryl, morpholinyl, pyrrolidinyl, pyridyl, quinonylmethyl and

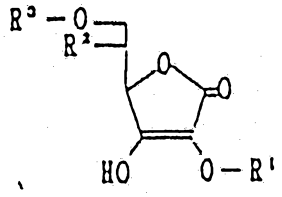
.../2

chroman-2-yl; R^2 is hydrogen or hydroxyl; R^3 is hydrogen or acyl of C_{1-20} fatty acid, benzoic acid, thienylacetic acid or nicotinic acid which may be substituted with halogen C_{1-3} alkyl, C_{1-3} alkoxy or hydroxy, and R^3 and hydroxyl of R^2 may form



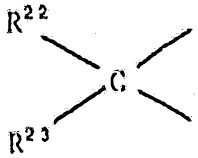
wherein R^{22} and R^{23} are independently hydrogen or C_{1-3} alkyl or R^{22} and R^{23} form $-(CH_2)_n-$ and n is 4 or 5, or a salt thereof, and a pharmaceutically acceptable carrier, vehicle or diluent therefor.

8. An ascorbic acid derivative of the formula:



[II]

wherein R^1 is substituted benzyl, phenacyl, cycloalkylmethyl or C_{1-22} alkyl which is substituted with hydroxyl or benzyloxy; R^2 is hydrogen or hydroxyl; R^3 is hydrogen or acyl of C_{1-20} fatty acid, benzoic acid, thienylacetic acid or nicotinic acid which may be substituted with halogen C_{1-3} alkyl, C_{1-3} alkoxy or hydroxy, and R^3 and hydroxyl of R^2 may form



wherein R^{22} and R^{23} are independently hydrogen or C_{1-3} alkyl or R^{22} and R^{23} form $-(CH_2)_n-$ and n is 4 or 5, or a salt thereof, and a pharmaceutically acceptable carrier, vehicle or diluent therefor.

599029

Form 10

PATENTS ACT 1952

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE

Short Title:

Int. Cl:

Application Number: 57350/86
Lodged:

Complete Specification—Lodged:
Accepted:
Lapsed:
Published:

Priority:

Related Art:

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

TO BE COMPLETED BY APPLICANT

Name of Applicant: TAKEDA CHEMICAL INDUSTRIES, LTD.

Address of Applicant: 27, Doshomachi 2-chome, Higashi-ku, OSAKA 541, JAPAN

Actual Inventor: Shinji TERAO and Minoru HIRATA

Address for Service: GRIFFITH HASSEL & FRAZER
71 YORK STREET
SYDNEY, N.S.W. 2000, AUSTRALIA

Complete Specification for the invention entitled: ASCORBIC ACID DERIVATIVES, PRODUCTION AND USE THEREOF

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

* Note: The description is to be typed in double spacing, pica type face, in an area not exceeding 250 mm in depth and 160 mm in width, on tough white paper of good quality and it is to be inserted inside this form.

14899/78—L

Printed by C. J. Thompson, Commonwealth Government Printer, Canberra

Ascorbic Acid Derivatives, Production and Use Thereof

This invention relates to ascorbic acid derivatives useful for prophylaxis and improvement of disorders in the circulatory system, a method for producing them and pharmaceutical compositions containing same.

Diseases of heart, brain, kidney, etc., which are often observed in adults, are mainly caused by disturbances and destruction of cells or tissues due to ischemia as a basal pathologic state, to result in hemostasia leading to suspension of supplying energy source. The morbidity rate of, for example, ischemic heart diseases, ischemic cerebral diseases, ischemic renal disturbances, ischemic gastrointestinal ulcers, has recently increased with the development of highly civilized society, and of the society holding high rates of persons of advanced age, and these diseases have become major factors in mortality rate in advanced countries.

Recently, it has been revealed that biologically activated oxygen species or reactive organic radical species play an important role in aggravation of lesions in ischemic tissues (i.e. lowering of cell function, disturbances, destruction, necrosis of cells, etc.)

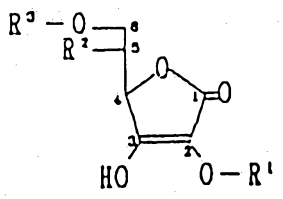
[I. Fridovich, Annual Review of Pharmacology and Toxicology 23, 239 (1983); J. M. McCord, The New England Journal of Medicine, 312, 159 (1985); K. P. Burton, J. M. McCord and G. Ghai, American Journal of Physiology, 246, H776 (1984)]. As the active oxygen species or reactive organic radical species in living system are considered, among others, superoxide anion radical ($O_2^{\cdot-}$), hydroxyl radical (.OH), singlet oxygen ($^1O_2$), and peroxide radical (ROO.). Especially, relationship between the formation of $O_2^{\cdot-}$ in a living system and the subsequent damages of cells or tissues caused by the reactive oxygen species have important meanings in ischemic disorders. Especially, it is considered that excess generation of $O_2^{\cdot-}$ in developing tissue damages after blood reperfusion at the site of ischemic lesion or after ischemia has an important significance.

It has been known that superoxide dismutase effectively acts to scavenge $O_2^{\cdot-}$ specifically, protects against tissue damages and alleviates tissue disturbances after reperfusion of the site of ischemia or after ischemia [D. N. Granger, G. Rulili, J. M. McCord, Gastroenterotogy, 81, 22 (1981)]. Also, it has been reported that such compounds as ascorbic acid, α-tocopherol, cysteine and reduced glutathione have an activity to scavenge free radicals, and that these compounds could prevent lesions in tissues, which are seemed to be caused by free radicals in pathological conditions

[I. Fridovich, Science, 201, 875 (1978)].

Based on the fundamental studies so far made, revealing that reactive oxygen species and organic radicals play a significantly important role in causing tissue disturbances in a living system, the present inventors have conducted research work for finding out a novel type of pharmaceuticals excellent pharmacologically as well as pharmaceutically aiming at scavenging reactive oxygen species and organic radicals. As the result, the present inventors found that 2-O-substituted ascorbic acid derivatives and homologs thereof showed, in experiments in vitro and in various animal test models, strong actions to scanvenge reactive oxygen species and organic radicals, and that they controlled ischemic heart diseases, disturbances in cerebral function or renal disorders, thus accomplishing the present invention.

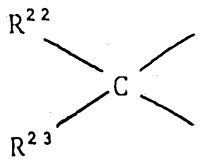
The present invention relates to a method of treatment of mammals, using a pharmaceutical composition, for prophylaxis and improvement of disorders in functions of the circulatory system, wherein the pharmaceutical composition contains an ascorbic acid derivative of the formula;



[I]

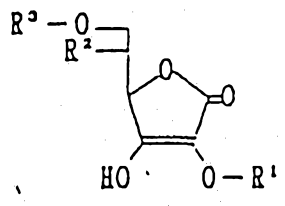
AUSTRALIAN PATENT OFFICE LS

wherein R^1 is straight-chain or branched alkyl having 1 to 22 carbon atoms which may be substituted with a member selected from a group consisting of hydroxyl, carboxyl, aminocarbonyl, vinyl, ethynyl, cycloalkyl, aryl, morpholinyl, pyrrolidinyl, pyridyl, quinonylmethyl and chroman-2-yl; R^2 is hydrogen or hydroxyl; R^3 is hydrogen or acyl of C_{1-20} fatty acid, benzoic acid, thienylacetic acid or nicotinic acid which may be substituted with halogen, C_{1-3} alkyl, C_{1-3} alkoxy or hydroxy, and R^3 and hydroxyl of R^2 may form



wherein R^{22} and R^{23} are independently hydrogen or C_{1-3} alkyl or R^{22} and R^{23} form $-(CH_2)_n-$ and n is 4 or 5, or a salt thereof, and a pharmaceutically acceptable carrier, vehicle or diluent therefor.

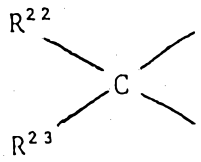
One aspect of the present invention comprises; using a pharmaceutical composition containing an ascorbic acid derivative representable by the formula;



[II]

AUSTRALIAN PATENT OFFICE LS

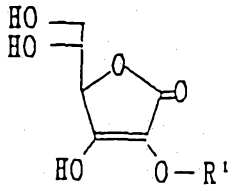
wherein R^1 is substituted benzyl, phenacyl, cycloalkylmethyl or C_{1-22} alkyl which is substituted with hydroxyl or benzyloxy; R^2 is hydrogen or hydroxyl; R^3 is hydrogen or acyl of C_{1-20} fatty acid, benzoic acid, thienylacetic acid or nicotinic acid which may be substituted with halogen C_{1-3} alkyl, C_{1-3} alkoxy or hydroxy, and R^3 and hydroxyl of R^2 may form



wherein R^{22} and R^{23} are independently hydrogen or C_{1-3} alkyl or R^{22} and R^{23} form $-(CH_2)_n-$ and n is 4 or 5, or a salt thereof, and a pharmaceutically acceptable carrier, vehicle or diluent therefor.

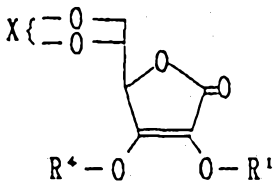
AUSTRALIAN PATENT OFFICE LS

a method for producing an ascorbic acid derivative representable by the general formula;



[Ia]

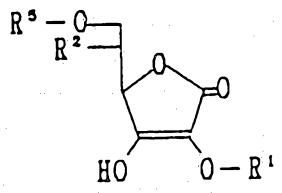
[wherein R^1 stands for other than an organic residue having a molecular weight of from 15 to 400 exclusive of substituted benzyl, phenacyl, cycloalkylmethyl and C_{1-22} alkyl which is substituted with hydroxy or benzyloxy] or a salt thereof, characterized by subjecting a compound representable by the formula;



[III]

[wherein R^1 is as defined above; R^4 stands for a group cleavable by hydrolysis or reduction; and X stands for two hydrogens, acetal residue or ketal residue] to hydrolysis or acid hydrolysis, followed by reduction,

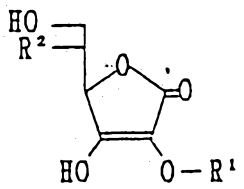
a method for producing an ascorbic acid derivative representable by the general formula;



[Ib]

[wherein R^1 and R^2 are as defined above; and R^5 stands for acyl or optionally substituted phosphono]

characterized by subjecting an ascorbic acid derivative representable by the general formula;

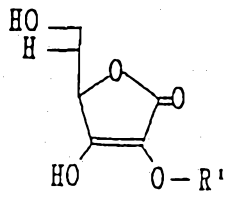


[IV]

[wherein R^1 and R^2 are as defined above]

to acylation or phosphorylation, and in case of acylation being conducted, followed by, when necessary, acyl migration or deacylation,

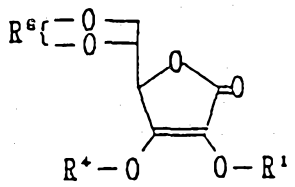
a method for producing an ascorbic acid derivative representable by the formula;



[Ic]

[wherein R^1 is as defined above],

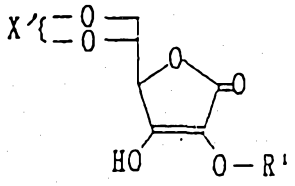
characterized by subjecting a compound representable by the formula;



[V]

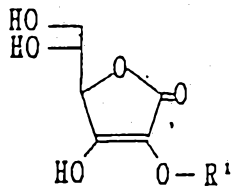
[wherein R^1 and R^4 are as defined above; and R^6 stands for acetal residue, ketal residue or O=S< group] to dehydration, then reduction, followed by, when necessary, hydrolysis, and

a method for producing an ascorbic acid derivative representable by the formula;



[Id]

[wherein X' stands for acetal residue or ketal residue, and R^1 is as defined above] characterized by subjecting an ascorbic acid derivative representable by the formula;



[Ia]

[wherein R^1 is as defined above] to acetalization or ketalization.

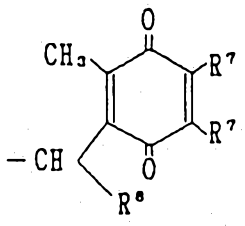
In the above general formulae, the organic residue having a molecular weight of from 15 to 700 as represented by R^1 includes, for example, straight-chain or branched alkyl groups optionally having substituents.

The above straight-chain or branched alkyl groups having a molecular weight of from 15 to 700 optionally having substituents is preferably that having 1 to 22 carbon atoms, more preferably 9 to 20 carbon atoms, further preferably straght-chain alkyl group having 14 to 20 carbon atoms.

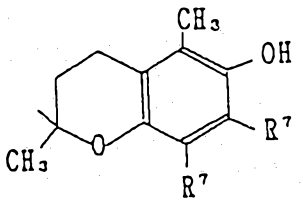
Examples of such alkyl group include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl, n-dodecyl, n-tridecyl, n-tetradecyl, n-pentadecyl, n-hexadecyl, n-heptadecyl, n-octadecyl, n-nonadecyl, n-eicosyl, n-heneicosyl and n-docosyl.

The number of methylene groups in the straight-chain or branched substituted alkyl group having a molecular weight of from 15 to 700 is preferably 1 ∿ 22.

The substituents of the above alkyl group are exemplified by optionally substituted hydroxyl groups, optionally substituted amino groups, optionally substituted carboxyl groups, optionally substituted aminocarbonyl groups, optionally substituted vinyl groups, optionally substituted ethynyl groups, optionally substituted cycloalkyl groups, optionally substituted aryl groups, optionally substituted heterocyclic groups, quinoyl representable by



or chroman-2-yl representable by

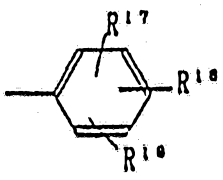


[wherein R^7 stands for methyl group, methoxy group, and the two R^7's form -CH=CH-CH=CH- group; and R^8 stands for phenyl, naphthyl, thienyl or pyridyl].

As the optionally substituted hydroxyl groups are mentioned those representable by the formula; $-O-R^9-$ [wherein R^9 stands for hydrogen, C_{1-3} alkyl or phenyl].

As the optionally substituted amino groups are mentioned those representable by the formula; $-N\begin{matrix}R^{10}\\R^{11}\end{matrix}$ [wherein R^{10} and R^{11} independently stand for hydrogen, C_{1-3} alkyl, phenyl or p-hydroxyphenyl]. As the optionally substituted carboxyl groups are mentioned those representable by the formula; $-CO-O-R^{12}$ [wherein R^{12} stands for hydrogen, C_{1-3} alkyl or phenyl]. As the optionally substituted aminocarbonyl groups are mentioned those representable by the formula; $-CO-NH-R^{13}$ [wherein R^{13} stands for hydrogen, C_{1-3} alkyl, phenyl or p-hydroxyphenyl]. As the optionally substituted vinyl groups are mentioned those representable by the formula; $-CH=C\begin{matrix}R^{14}\\R^{15}\end{matrix}$ [wherein R^{14} and R^{15} independently hydrogen, phenyl, p-methoxyphenyl, 3-pyridyl or 3,4-methylene dioxyphenyl]. As the optionally substituted ethynyl groups are mentioned those representable by the formula; $-C\equiv C-R^{16}$ [where in R^{16} stands for C_{1-6} alkyl].

The cycloalkyl group in the optionally substituted cycloalkyl groups is preferably those of C_{3-6}, exemplified by cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. The cycloalkyl may optionally have $1 \sim 3$ substituents exemplified by carboxyl, hydroxyl or C_{1-6} alkyl. Examples of the optionally substituted aryl group include a group representable by the formula;



[wherein R^{17}, R^{18} and R^{19} independently stand for hydrogen, C_{1-3} alkyl, C_{1-3} alkoxy, halogen, ethoxycarbonylethenyl, phenyl, carboxyl, carboxymethyl or 1-carboxyethyl] or naphthyl optionally substituted with 1 to 3 of C_{1-3} alkyl, C_{1-3} alkoxy, halogen, carboxy or acetyl.

The C_{1-6} alkyl is exemplified by methyl, ethyl, n-propyl, isopropyl, n-butyl, n-pentyl or n-hexyl.

The C_{1-3} alkyl is exemplified by methyl, ethyl, n-propyl or isopropyl.

The C_{1-3} alkoxy is exemplified by methoxy, ethoxy, n-propoxy or isopropoxy.

The halogen is exemplified by chlorine, bromine, fluorine or iodine.

Examples of the hydroxyl group having the said substituent include C_{1-3} alkoxy of methoxy, ethoxy, propoxy, isopropoxy and phenoxy. Examples of the amino group having the said substituent included mono C_{1-3} alkyl or di C_{1-3} alkyl of methylamino, dimethylamino, ethylamino, propylamino, isopropylamino, phenylamino and p-hydroxyphenylamino. Examples of the carboxyl group having the said substituent include methoxy, carbonyl, ethoxycarbonyl and

phenoxycarbonyl. Examples of the aminocarbonyl group having the said substituent include methylaminocarbonyl, dimethylaminocarbonyl, isopropylaminocarbonyl, phenylaminocarbonyl and p-hydroxyphenylaminocarbonyl.

Examples of the vinyl group having the said substituent include propenyl, butenyl, pentenyl, hexenyl, heptenyl, 1,1-diphenylethenyl, 1-phenyl-1-(3-pyridyl)ethenyl and 1-phenyl-1-(2-thienyl)ethenyl. Examples of the ethynyl group having the said substituent include methylethynyl, ethylethynyl and n-pentylethynyl. Examples of the cycloalkyl group having the said substituent include cyclopropyl, cyclopentyl, cyclohexyl, 1-carboxycyclopropyl, 2-carboxycyclopropyl, 1-carboxycyclopentyl, 1-carboxycyclohexyl and 4-carboxycyclohexyl. Examples of the aryl group having the said substituent include phenyl, 1- or 2-naphthyl, 2-, 3- or 4-monomethylphenyl, 2-, 3- or 4-monomethoxyphenyl, 2-, 3- or 4-monomethoxyphenyl, 2-, 3 or 4-monohalogenophenyl (halogen atom means chlorine, bromine or fluorine atom), 2,3-methylenedioxyphenyl, 3,4-dimethylphenyl, 3,4-dimethoxyphenyl, 4-(ethoxycarbonylethenyl) phenyl, 4-isopropylphenyl, 4-methoxycarbonylphenyl, 3,4,5-trimethylphenyl, 3,4,5-trimethoxyphenyl, 4-biphenyl; 4-carboxyphenyl, 4-carboxymethylphenyl, and 4-(1-carboxyethyl)phenyl. Examples of the heterocyclic group having the said substituent include 2-, 3- or 4-pyridyl, 2- or 3-thienyl, morpholine, pyrrolidinyl, piperidinyl, piperazinyl, 4-phenylpiperazinyl,

4-(p-flurophenyl)piperazinyl, 4-diphenylmethylpiperazinyl and 4-(p-methoxyphenyl)piperazinyl, which may have 1-3 substituents exemplified by C_{1-3} alkyl, carboxyl, hydroxyl group, phenyl, halogen, carboxymethyl or benzoyl.

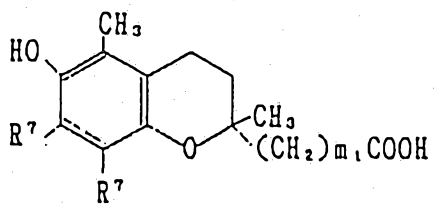
In the above-mentioned general formulae, the organic residue having a molecular weight of from 72 to 700 as represented by R^1 includes, for example, straight-chain or branched alkyl groups optionally having substituents.

The alkyl group in the said optionally substituted straight-chain or branched alkyl groups having the molecular weight of from 72 to 700 is preferably those whose carbon number is from 6 to 22, more preferably those whose carbon number is from 11 to 20, as exemplified by n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl, n-dodecyl, n-tridecyl, n-tetradecyl, n-pentadecyl, n-hexadecyl, n-heptadecyl, n-octadecyl, n-nonadecyl, n-eicosyl, n-heneicosyl, n-docosyl, etc.

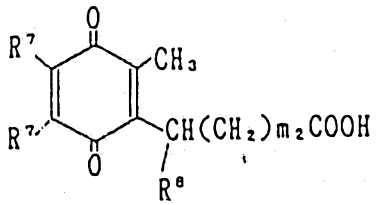
The number of methylene groups in the above-mentioned straight-chain or branched substituted alkyl group having a molecular weight of from 15 to 700 is preferably 1 ∿ 22.

As the substituents in the said substituted straight-chain or branched alkyl group having a molecular weight of from 72 to 700, are mentioned the same substituents in the afore-said optionally substituted straight-chain or branched alkyl group having a molecular weight of from 15 to 700.

The acyl group representable by R^3 and R^5 in the above general formulae include straight-chain or branched fatty acid whose carbon number is 1 ∿ 22, optionally substituted benzoic acid, optionally substituted thienylacetic acid, optionally substituted phenylacetic acid, dicarboxylic acid, acyl groups derivable from carboxylic acid representable by the formulae;



or



[wherein R^7 and R^8 are as defined above, m_1 denotes an integer of 1 or 2 and m_2 denotes an integer of 2 to 8] or an optionally substituted aminocarbonyl group.

Examples of the fatty acid include C_{1-20} fatty acid of formic acid, acetic acid, propionic acid, valeic acid, butyric acid, hexanoic acid, heptanoic acid, octanoic acid, nonanoic acid, decanoic acid, undecanoic acid, tridecanoic acid, tetradecanoic acid, pentadecanoic acid, hexadecanoic acid, octadecanoic acid, nonadecanoic acid, eicosanoic acid, isopropionic acid, etc.

Examples of the substituents of the said optionally substituted benzoic acid include C_{1-3} alkyl, C_{1-3} alkoxy, methylenedioxy, halogen, etc.

The substituent of the optionally substituted 2- or 3-thienyl acetic acid is exemplified by C_{1-3} alkyl. Examples of the substituent of the optionally substituted phenyl acetic acid include C_{1-3} alkyl, C_{1-3} alkoxy, methylenedioxy, halogen, etc. The substituents of the optionally substituted phenyl group thienyl group or naphthyl group representable by R^{17} are exemplified by C_{1-3} alkyl, C_{1-3} alkoxy, methylenedioxy, halogen, etc. The substituent of the said optionally substituted aminocarbonyl group is exemplified by optionally mono- or di-substituted C_{1-6} lower alkyl group or monophenyl group. Examples of the C_{1-6} lower alkyl group include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, n-pentyl, n-hexyl, etc. The substituents are exemplified by phenyl, naphthyl, pyridyl, imidazolyl, etc.

As the acyl group derivable from dicarboxylic acid is mentioned those of monoester type. Examples of the dicarboxylic acid include malonic acid, succinic acid, glutaric acid, adipic acid, etc.

As the said C_{1-6} lower alkyl are exemplified methyl, ethyl, n-propyl, isopropyl, n-butyl, n-pentyl, n-hexyl, etc.

As the said C_{1-3} alkyl are exemplified methyl, ethyl, n-propyl, isopropyl, etc.

As the said alkoxy are exemplified methoxy, ethoxy, n-propoxy, isopropoxy, etc.

As the said halogen are exemplified chlorine, bromine, iodine and fluorine. In the above formulae, the substituents at the optionally substituted phosphono group as represented by R^3 are preferably mono-substituted ones which are exemplified by those representable by the formula $-(CH_2)n-R^{24}$ [wherein n denotes an integer of 1 - 3 and R^{24} stands for a heterocyclic group having amino, dialkylamino, trialkylamino or nitrogen].

Preferable examples of the alkyl at the dialkylamino and trialkylamino as represented by R^{24} are methyl, ethyl, n-propyl and isopropyl.

As the nitrogen-containing heterocyclic ring as represented by R^{24} are exemplified 1-pyridinio, 1,3-thiazolinio, piperazinyl, piperidino, morpholino, pyrrolidinyl, etc.

In the above general formula, examples of the cleavable groups by hydrolysis as represented by R^4 are methoxymethyl, ethoxymethyl, benzyloxymethyl, 2-tetrahydropyranyl, trimethylsilyl, dimethyl tertiary butylsilyl, etc., and examples of the cleavable groups by reduction as represented by R^4 are benzyl, p-methoxybenzyl, etc.

As the above-mentioned acetal residue, groups representable by the formula $R^{21}-CH<$ [wherein R^{21} stands for C_{1-3} alkyl, phenyl or p-methoxyphenyl] are mentioned, and, as the ketal residue, groups representable by the formula $\begin{matrix} R^{22} \\ R^{23} \end{matrix}>C<$ [wherein R^{22} and R^{23} independently stand

for hydrogen or C_{1-3} alkyl, or R^{22} and R^{23} form $-(CH_2)_2-$ (wherein a denotes 4 or 5)] are mentioned.

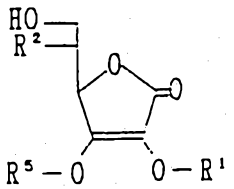
Examples of the above-mentioned C_{1-3} alkyl include methyl, ethyl, n-propyl or isopropyl.

In case where Compound [I] or [II] is capable of forming a salt, it may be formed into a salt, and the salt is exemplified by inorganic salt of sodium salt, potassium salt, ammonium salt, hydrochloride, sulfate, etc., or it may form an internal salt.

Compound [Ia] i.e. Compound [I] wherein R^2 is hydroxyl group and R^3 is hydrogen, when the protecting group in Compound [III] is cleavable by hydrolysis, can be produced by subjecting Compound [Ia] to acid hydrolysis to remove the acetal residue or ketal residue at the 5-, and 6-positions and the protecting group at the 3-position simultaneously.

In case where the protecting group R^4 at the 3-position of Compound [III] is cleavable by reduction, Compound [Ia] can be produced by subjecting Compound [III] to acid hydrolysis to remove the acetal residue or ketal residue at the 5,6-position, followed by removing the protecting group at the 3-position by catalytic reduction.

Compound [Ib], i.e. Compound [I] wherein R^3 is acyl group, can be produced by subjecting Compound [IV], i.e. Compound [I] wherein R^3 is hydrogen, to acylation, or, when a compound representable by the general formula;



[VI]

[wherein R^1, R^2 and R^5 are as defined above, and R^5 stands for acyl group] is produced by the acylation, by further subjecting the compound to acyl-rearrangement reaction. Compound [Ic], i.e. Compound [I] wherein R^2 and R^3 are both hydrogen, can be produced by subjecting Compound [V] to hydrolysis under basic conditions, followed by catalytic reduction and, when necessary, acid hydrolysis.

The above acid hydrolysis is carried out for about 1-2 hours at about 10-80°C in water or an organic solvent e.g. methanol, ethanol, dioxane, tetrahydrofuran, 1,2-dimethoxyethane, or an aqueous mixture thereof.

The above catalytic reduction is carried out for about 4-10 hours at about 10°C-100°C in an organic solvent e.g. methanol, ethanol, ethyl acetate, dioxane, 1,2-dimethoxyethane, etc., in the presence of, for example, palladium, palladium-carbon, platinum black, palladium chloride, platinum oxide, etc.

In the above acylation, as the reactivity of the enolic hydroxyl group at the 3-position is higher than

that at the 6-position, the former hydroxyl group is first acylated. The 3-O-acyl derivative is, depending on the kinds of acyl group, readily rearranged internally under weakly basic conditions, to lead to a 6-O-acyl derivative [VI]. 3-O-Acyl derivative [VI] exists as an intermediate as well, but it is readily susceptible to internal migration or hydrolysis, thus being chemically unstable compound. Accordingly, a 6-O-acyl derivative can be produced by subjecting a 3-O-acyl derivative to internal migration. The internal migration completes in about 1-10 hours at about 20-100°C in the presence of a weak base [e.g. pyridire, sodium carbonate, buffer solution (pH about 7-8)].

The above acylation is usually conducted by a conventional method. As the solvent is often used acid chloride or anhydride of carboxylic acid (including mixed acid anhydride), and the reaction is carried out in the presence of a base e.g. pyridine, triethylamine, potassium carbonate, sodium carbonate, sodium hydrogencarbonate, etc., at about -10° - 50°C. The reaction time is, in most cases, within about 1-10 hours.

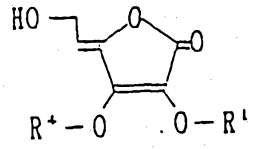
In the above phosporylation, the phosphorylating agent to be employed is exemplified by 2-cyanoethylphosphate-dicyclohexylcarbodiimide, di-p-nitrobenzylphosphorylchloride, dioxane diphosphate, dimorpholyl phosphoric acid chloride, pyrophosphoryltetrachloride, etc.

In the above sulfonation, the surfonating agent to be employed is exemplified by sulfuric anhydride (SO_3), sulfuric anhydride pyridine (SO_3-C_5H_5N), sulfuric acid dioxane ($SO_3OC_4H_8O$), sulfuric anhydride dimethylformamide [SO_3-$HCON(CH_3)_2$], sulfuric anhydride triethylamine [SO_3-$N(C_2H_5)_3$], etc.

In the above phosphorylation and sulfonation, the solvent to be employed is exemplified by dioxane, dimethylformamide, chloroform, methylene chloride, etc. The reaction temperature is within the range of from -10°C to -50°C, and the reaction time is about 1-10 hours. To lead the compound obtained to a salt thereof, a conventional means is employed. Elimination of the acyl group at the 3-position is conducted by the addition of an equimolar amount of sodium hydrogencarbonate or pyridine, and hydrolysis is conducted at room temperature. The reaction time is about 1-6 hours.

The dehydration is completed in about 1-4 hours at a temperature range of about 30-80°C in an organic solvent such as methylene chloride, chloroform, dioxane, tetrahydrofuran, benzene, etc., in the presence of an organic base e.g. 1,5-diazabicyclo[4,3,0]-5-nonene, 1,4-diazabicyclo[2,2,2]octane, 1,8-diazabicyclo[5,4,0]-7-undecene, pyridine, triethylamine.

By conducting the dehydration, a compound of the general formula [VI'];



[VI']

[wherein R^1 and R^4 are as defined above] can be obtained.

By subjecting compound [VI'] to reduction, followed by, when necessary, hydrolysis, Compound [Ic] can be produced. The said reduction and hydrolysis can be conducted as mentioned above.

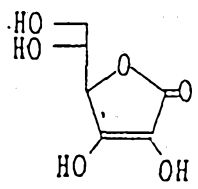
The reaction for producing Compound [Id] by acetalization or ketalization of Compound [Ia] is conducted by allowing the starting compound to react with ketone or aldehyde, e.g. acetone, benzaldehyde, cyclopentanone, cyclohexanone, etc. As the reaction solvent are employed toluene, tetrahydrofuran, chloroform, diethylether, dichloromethane, dichloroethane, etc. The reaction temperature ranges from about 15°C to 150°C, and the reaction is conducted in the presence of an acid catalyst. The catalyst is exemplified by acetylchloride, sulfuric acid, p-toluenesulfonic acid, camphorsulfonic acid. The reaction time ranges from about 1 to 24 hours.

Thus produced ascorbic acid derivatives [I] can be separated and collected by per se known separation and purification means (e.g. column chromatography using

silica-gel, polystyrene resins, activated carbon, reverse phase system, etc., recrystallization, etc.).

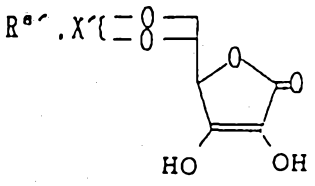
Compounds employable as the starting materials in the method of this invention can be produced by, for example, the following reaction steps.

[A] - Method for producing Compound [III'], i.e. Compound [III] wherein X is acetal or ketal residue, and Compound [V'], i.e. Compound [V] wherein R^6 is acetal residue or ketal residue:



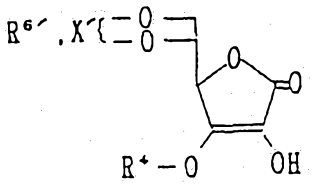
{Ascorbic acid, d,ℓ-ascorbic acid, isoascorbic acid

Acetalization, ketalization

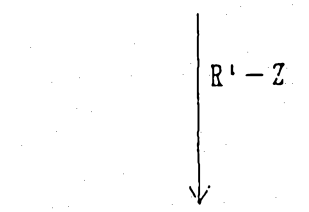


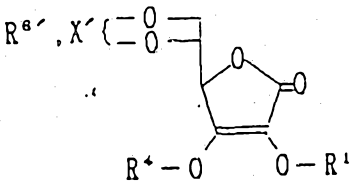
[VII]

R^4-Y



[VIII]





[V'], [III']

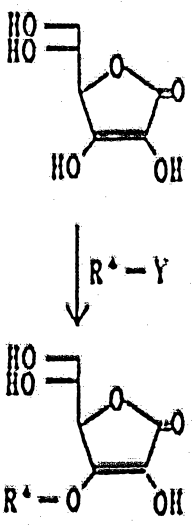
In the above formulae, X' and $R^{6'}$ stand for acetal or ketal residue.

In case of ascorbic acid being used as the starting material, the ascorbic acid is first acetalized or ketalized to produce Compound (VII). This reaction is conducted by allowing ascorbic acid to react with ketone or aldehyde e.g. acetone, benzaldehyde, cyclopentanone, cyclohexanone, etc. As the reaction solvent are employed, among others, tetrahydrofuran, chloroform, diethylether, dichloromethane or dichloroethane. The reaction temperature ranges from room temperatures to 60°C, and the reaction is conducted in the presence of an acid catalyst. Examples of the catalyst include acetylchloride, sulfuric acid, p-toluenesulfonic acid and camphorsulfonic acid. The reaction time ranges from 4 to 24 hours. Subsequently, Compound [VII] is allowed to react with a compound representable by the formula; R^4-Y [wherein R^4 is as defined above, and Y stands for halogen (e.g. chlorine, bromine)] (e.g. chloromethyl-methylether, chloromethylethylether, benzylchloride, benzylbromide) in dimethylformamide, dimethylsulfoxide (DMSO), hexamethylphosphoramide or tetrahydrofuran, either singly or a solvent mixture thereof in the presence of an inorganic base such as potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide and sodium hydrogen-carbonate to produce Compound (VIII]. The reaction temperature ranger from 0°C to 40°C (preferably 25°C). The reaction goes to conclusion within 1 to 18 hours.

Then, Compound (VIII) thus obtained is allowed to react with a compound representable by the formula; R^1-Z [wherein R^1 is as defined hereinbefore, and Z stands for halogen (e.g. chlorine, bromine)] in a solvent such as dimethylformamide, dimethylsulfoxide, hexamethylphosphoramide or tetrahydrofuran, solely or as a solvent mixture thereof, in the presence of an inorganic base (e.g. sodium hydroxide, potassium hydroxide, sodium carbonate and potassium carbonate) at a temperature of 10 to 60°C for 1 to 18 hours to produce Compound [III'] or [V'].

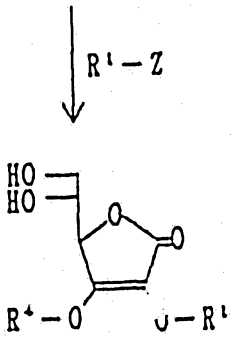
Compound [III"], i.e. Compound (III) wherein X stands for two hydrogen atoms, can be produced by subjecting Compound [III'] to hydrolysis similar to that mentioned hereinbefore.

[3]-Compound [III"], e.e. Compound [III] wherein X is two hydrogen atoms, can be produced by the following process.



Ascorbic acid
Isoascorbic acid

[IX]



[III''], [X]

In the above method, ascorbic acid or isoascorbic acid is employed as the starting material, and the hydroxyl group of its 3-position is allowed to react, in accordance with the conventional method, with methoxymethyl chloride, ethoxymethyl chloride, benzylbromide, trimethylsilyl chloride, dimethyl tertiary silyl chloride, etc. to give a 3-O-ether compound (IX), then, thus obtained compound [IX] is allowed to react with a compound representable by the formula; R^1-Z [wherein R^1 and Z are as defined hereinbefore] within the temperature range of about 10 ∿ 60°C for about 1 to 20 hours in dimethylformamide, dimethylsulfoxide, hexamethyl phosphoramide, tetrahydrofuran, dioxane, etc., either singly or as a solvent mixture, in the presence of an inorganic base (e.g. potassium carbonate, sodium carbonate, etc.) to give Compound [X].

[C]- Method for producing Compound [V'], i.e. Compound [V] wherein R^6 stands for O=S< group:

The above compound is produced by allowing thionyl chloride to react with Compound [X].

The reaction is carried out in a solvent, for example tetrahydrofuran, dimethylformamide, methylene chloride, etc. in the presence of an organic base, for example, triethylamine, pyridine, 1,8-diazabicyclo[5,4,0]-7-undecene. The reaction is conducted at about 0 ∿ 30°C for about 1 ∿ 6 hours.

Compounds [III] and [V] as produced in accordance with the afore-mentioned methods are useful as intermediates for the synthesis of, for example, Compound [I].

Compound [I] and salts thereof show lipid per-oxidation inhibitory action in the experiments in vitro employing a stable radical or brain homogenates, and, in the ischemia-reperfusion model in the heart of rats or the ischemic brain model in rats or the renal failure model in rats due to oxygen free radicals, they show actions of preventing or improving the respective functional disorders, while they show remarkably low toxicity and no side effects. Compound [I] and salts thereof show therapeutic, prophylactic and improving actions against various functional disorders, for example, ischemic heart diseases (arrhythmia, coronary vasospasm, necrosis of cardiac tissue, myocardial infarction, etc.), subarachnoidal hemorrage, ischemic disorders of cerebral tissue (e.g. cerebral infarction, dementia,

senile dementia, etc.), ischemic renal disorders, intestinal ischemic (e.g. intestinal ulcer, etc.), thus being useful as preventing and improving agents of functional disorders in the circulatory system.

Specific examples of the use as the above preventing and improving agents of functional disorders in the circulatory system include improving agents of circulatory system, improving agents of renal functions, therapeutic agents of stress intestinal ulcer, etc., e.g. agents of anti-arrhythmia, anti-myocardiac infarction, anti-cerebral infarction, preventing senile dementia, therapy and improvement after subarachmoidal hemorrhage.

The compounds of this invention are low in toxicity (e.g. in acute toxicity to mice, no test animals were killed by oral administration at a dose of 1000 mg/kg), and Compound [I] can be safely administered orally or non-orally as pharmaceutical compositions [e.g. tablets, capsules (including soft-capsules and micro-capsules), liquids, suppositories, injections, preparations for nasal inhalation] prepared by mixing with per se conventional phamacologically acceptable carriers, excipients, diluents, etc. in accordance with per se known methods. While the dosage varies with the subjects administration routes, symptoms, etc., it is usually, when administered to the above-mentioned mammals, about 0.1 mg/kg ∿ 50 mg/kg

body weight, preferably about 0.5 mg/kg ∿ 20 mg/kg body weight 1 ∿ 3 times a day.

When Compound [I] is administered non-orally, for examples as a suppository, about 5 mg ∿ 10 mg/kg in terms of Compound [I], 1 ∿ 2 times a day. As the injections, it is desirable to use, in terms of Compound [I], about 0.1 mg/kg ∿ 5 mg/kg 1 ∿ 2 times a day.

For preparation of the above-mentioned compositions for oral use, a binding agent (e.g. hydroxypropyl cellulose, hydroxymethylpropylmethylcellulose, macrogol, etc.), a disintegrator (e.g. starch, carboxymethyl cellulose calcium, etc.), an excipient (e.g. lactose, starch, etc.), a lubricant (e.g. magnesium stearate, tale, etc.), etc. may be suitably incorporated.

When a composition of non-oral use, for example, a injectable preparation, an isotonizing agent (e.g. glucose, D-sorbitol, D-mannitol, sodium chloride, etc.), an antiseptic (e.g. benzylalcohol, chlorobulanol, methyl para-hydroxybenzoate, propyl para-hydroxybenzoate, etc.), a buffer (e.g. phosphate buffer, sodium acetate buffer, etc.), etc. may be suitably incorporated.

Brief Description of the Drawing

Figure 1 shows the result of oxidation inhibitory activity disclosed in Experiment 1.

The experiment examples, reference examples and working examples are given below to illustrate the present invention more specifically.

Experiment 1

Oxidation inhibitory activity determined with the use of a stable radical:

In accordance with the method of M. S. Brois [Nature, 181, 1199, 1958], the activity to reduce a stable free radical, α, α-diphenyl-β-picryl hydrazyl (DPPH), was determined, which was used as an index of the oxidation inhibitory activity. More concretely, a test drug [i.e., the compound [I] wherein R^1=-$(CH_2)_{17}CH_3$, R^2= OH, R^3=H, which is sometimes referred to as "compound (1-12)"] was added to 3 ml of 0.1 mM DDPH ethanol solution. Then, 20 minutes later, the absorbance at a wavelength of 517 nm was measured with the use of a spectrophotometer. The difference in absorbance between a sample solution and reference solvent [not more than 0.5% of DMF] was taken as the reduction activity.

The results of the experiment are shown in Fig. 1, where - ● - indicates the results with the above test drug, - O - the results with vitamin E, and - ▲ - the results with vitamin C.

The above test drug was found to reduce DDPH at

the concentration of not less than 10^{-5}M in a manner dependent upon the amount used. Vitamins C and E showed the activity equal to that of the test drug.

Experiment 2

Activity to inhibit lipid peroxide formation in rat brain tissue homogenate:

(i) Method:

Male SD rats (12-weeks old) were subjected to exsanguination under anesthesia with pentobarbital, then the brain was excised. The brain tissue was homogenized in a phosphate buffer solution (pH 7.4) to prepare a 5% homogenate. After incubation of the homogenate at 37°C for 1 hour, the amount of lipid peroxides formed therein was determined by thiobarbituric acid (TBA) method in accordance with the report of Ohkawa et al. on Analytical Biochemistry 95 351, 1979.

The test drug was added to the 5% homogenate before incubation so as to make the final concentration be 10^{-5}M. The activity to inhibit the formation of lipid peroxides was compared with that of the reference group to which was added the solvent (DMSO), and shown by % inhibition.

(ii) The results are shown in Table 1 below:

The activity to inhibit the formation lipid peroxides varies with the length of the side chain, when

the number (n) of the side-chain methylene groups in the general formula [I] was changed in the range of 7-21. When n is in the range of 13-19, the corresponding compounds showed higher activity, reaching 80% or higher in the inhibitory activity, which is more potent than that of vitamin E. As compared with the compound having at the 3-position a methylene chain whose n equals to 17, the compound (1-12) showed higher activity. In the same experimental system, vitamin C rather promoted the formation of lipid peroxides remarkably.

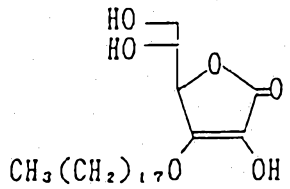
Table 1

Activities to inhibit lipid peroxide formation in rat brain tissue homogenates (TBA method)

Compound [I]	Inhibitory Effect (%)
$R^2=OH, R^3=H, R^1=-(CH_2)_7CH_3$	-6.6± 3.0
$R^2=OH, R^3=H, R^1=-(CH_2)_9CH_3$	40.0± 1.1
$R^2=OH, R^3=H, R^1=-(CH_2)_{11}CH_3$	55.7±26.5
$R^2=OH, R^3=H, R^1=-(CH_2)_{13}CH_3$	93.1± 5.3
$R^2=OH, R^3=H, R^1=-(CH_2)_{14}CH_3$	100.0± 0
$R^2=OH, R^3=H, R^1=-(CH_2)_{15}CH_3$	78.5±11.7
$R^2=OH, R^3=H, R^1=-(CH_2)_{17}CH_3$	88.6± 6.8
$R^2=OH, R^3=H, R^1=-(CH_2)_{19}CH_3$	95.4± 4.6
$R^2=OH, R^3=H, R^1=-(CH_2)_{21}CH_3$	38.1±16.6
Compounds having a group at the 3-position*	45.4± 8.7
Vitamin C	-71.6±36.8
Vitamin E	44.9±11.7

Note) The concentration of each compound is 10^{-5}M, and the number of experimental examples of each compound is 3. Inhibitory effects (%) are shown by mean values ± standard error.

Note) Compounds having a group at the 3-position:



Experiment 3

Effects to alleviate renal disorders in rats due to Fe^{3+} nitrilotriacetate:

(i) Method

Male SLC-Wistar rats (4-weeks old, 64∿85 g) were used. The animals were housed individually in metabolism cages and allowed free access to feed and water. Body weight, volume of urine and protein in urine (BIO-RAD method) were determined every day, and occult blood reaction was also examined (Labstick method). On the last day of the experiment, the kidney was excised and weighed.

The animals were orally administered once daily with test drugs or vehicles thereof (suspension in gum arabic), and, 40∿60 minutes later, were injected intraperitoneally with nitrilotriacetate (NTA) or Fe^{3+}-NTA. Fe^{3+}-NTA was used in a form of mixture (1:4, molar ratio), and the dosages were 5 mg/kg in terms of Fe^{3+} for 3 days and successively 10 mg/kg for 5 days.

Test drugs were compound (1-12), vitamin C and vitamin E, and the dosages were all 30 mg/kg.

(ii) Results

The results observed on the last day of the experiment

are shown in the following Tables 2 and 3.

In the animal groups administered with the vehicle, renal disorders due to Fe^{3+}-NTA were observed, and the weight of kidney remarkably increased and, in most of the animals, occult blood test was positive, and remarkable increases in urine volume and protein in urine were observed. In the groups administered with compound (1-12), renal disorders were alleviated, thus, as compared with the groups administered with vehicle, the weight of kidney was significantly less, and the urine volume and urinary protein were significatly less and, only in half of the test animals, occult blood was detected. Vitamin E showed substantially the same effects, but, in more than half of the test animals,occult blood test was positive. Vitamin C did not show significant effect for alleviating renal disorders.

Table 2

Effects on renal disorders due to Fe^{3+}-nitrilotriacetate (NTA)

Group	n	Body Weight (g)	Kidney Weight (mg)	Occult Blood Test
None*1	2	118	51	0/2
Vehicle*2	6	86.6±3.7	68.2±2.1	5/6
Compound (1-12)	6	95.5±3.0	56.5±2.0**	3/6
Vitamin C	6	89.2±4.1	64.5±1.7	5/6
Vitamin E	6	99.3±2.3	54.3±2.7**	4/6

Dosage of each test drug was 30 mg/kg, orally.

n: number of test animals

*1 None: Control animals not administered with Fe^{3+}-NTA

*2 Vehicle: Gum arabic suspension

Table 3

Effects on renal disorders due to Fe^{3+}-nitrilotriacetate (NTA)

Group	n	Volume of urine (ml/day)	Protein in urine (mg/day)
None	6	5.4±1.2	3.0±1.1
Vehicle	6	13.2±2.0	15.1±1.9
Compound (1-12)	6	7.4±1.3*	8.1±2.1*
Vitamin C	6	10.3±1.7	10.7±2.4
Vitamin E	6	9.0±1.0	6.3±1.4*

Dosage of each test drug was 30 mg/kg, orally.

n: number of test animals

None: Control animals not administered with Fe^{3+}-NTA

Vehicle: Gum arabic suspension

Experiment 4

Action to inhibit ventricular arrhythmias occurred during coronary artery occlusion-reperfusion in rat hearts

(i) Method

Male SD rats (9∿13 - weeks old, 250∿370 g) were used.

The animals were subjected to thoractonomy under artificial respiration while anesthesia was maintained by administering pentobarbital. The left anterior descending coronary artery was ligated with silk thread for 5 minutes, then the ligation was released to allow reperfusion, and animals were observed for 10 minutes. By recording standard limb lead II electrocardiograms, occurrence of ventricular arrhythmias was examined.

The animals were administered, under non-anesthesia, with test drugs as a gum arabic suspension at the dosage of 30 mg/kg at the time of about 90 minutes and of 20 mg/kg at the time of about 45 minutes (total: 50 mg/kg), or at the dosage of 10 mg/kg each (total: 20 mg/kg) at the time of about 90 minutes and about 45 minutes prior to closure of the coronary artery. The results are shown in Table 4 in terms of the total amount of the dosage.

(ii) Results

When reperfusion was permitted after the closure for 5 minutes of the left anterior descending coronary artery, ventricular arrhythmias, typically exemplified by occasionally occurring premature ventricular contractions (PVCs), ventricular tachycardia (VT) and ventricular fibrillation (VF), were observed. VT and VF were paroxysmally repeated, or sustained VF resulted in death.

In the group administered with the vehicle, VF and VT were observed in more than 90% of the animals, and the durations were respectively about 80 and 20∿30 seconds. Among the animals, 10∿25% were killed by occurrence of sustained VF.

In the groups administered with 20 and 50 mg/kg each of compound (1-12), occurrence of those arrhythmias was suppressed significantly and depending on the dosages. Even when the arrhythmias occurred, the period of time during which the symptom lasted was shortened. Consequently the mortality due to VF was low. Frequency of occasional PVCs was around 10 times/minutes in the groups of the vehicle, while, in the group administered with compound (1-12), the frequency was less significantly. On the other hand, no significant effects were observed by oral administration of vitamin C or E at the dosage of 50 mg/kg.

Table 4

Effects on ventricular arrhythmias observed when reperfusion was permitted after closure of the coronary artery in rat hearts.

Group	Ventricular fibrillation Incidence	Duration	Ventricular tachycardia Incidence	Duration	Extrasystole	Mortality
Control	7/8(88)	83.9±27.5	7/8 (88)	31.8±15.0	10.8±3.5	2/8 (25)
Compound (1-12) 50mg/kg	2/9* (22)	1.2± 0.8**	2/9* (22)	3.2± 2.6*	1.1±0.3**	0/9 (0)
Control	16/18 (89)	74.2±30.8	17/18 (94)	26.5± 6.8	11.8±4.0	2/18(11)
Compound (1-12) 20mg/kg	9/17*(53)	31.0±28.2	11/17 (65)	10.2± 3.2*	3.3±0.8**	1/17(6)
Control	17/18 (94)	74.1±36.0	17/18 (94)	16.6± 4.4	7.3±1.7	3/18(17)
Vitamin C 50mg/kg	6/6 (100)	9.7± 2.5	6/ 6(100)	19.0± 3.0	5.1±1.0	0/ 6(0)
Vitamin E 50mg/kg	6/10 (60)	43.4±36.0	7/10 (70)	22.3± 9.7	7.0±4.1	1/10(10)

* : $P < 0.05$, ** : $P < 0.01$, as compared with Control Group

Incidences of ventricular fibrillation and ventricular tachycardia are shown by the percentage of the number of animals presenting the symptoms relative to the number of animals subjected to the test, and the duration of the symptoms was shown in average ±SEM by seconds.

Extrasystole is shown by the number of systole/min, and the mortality is shown by the percentage of the number of animals killed relative to the number of animals subjected to the test.

Experiment 5

Inhibition of ischemic seizure due to ligation of bilateral common carotid arteries in SHR rats

i) Method

Male SHR rats (22-weeks old, about 360 g) were used. Under light anesthesia with ether, the animals were subjected to midline incision at the neck and the bilateral common carotid arteries were singled, then ligated to cause cerebral ischemia. Thereafter, the animals were allowed to awake from the anesthesia, and the behavior was observed for about 4 hours. The animals were orally administered with test drugs as a gum arabic suspension 60 minutes before the ligation of the bilateral common carotid arteries. The results are shown in Table 5.

ii) Results

When the bilateral common carotid arteries were ligated to cause cerebral ischemia, convulsion , an ischemic seizure, was observed after about 150 minutes in the vehicle group. The seizure was observed in about 90% of the rats within 180 minutes. But, in the group orally

administered with compound (1-12) at a dosage of 100 mg/kg, the appearance of the convulsion was significantly delayed by about 40 minutes. The incidence of appearance of the seizure within 180 minutes was significantly inhibited to 20%.

Table 5

Activity to inhibit ischemic convulsive seizure observed when bilateral common carotid arteries were ligated in SHR rats

		Ischemic convulsive seizure	
Group	n	Time (min)	Incidence ⓐ
Vehicle	41	151 4	36/41 (87.8%)
Compound (1-12)	5	199 13*	1/5* (20 %)

Compound (1-12): 100 mg/kg p.o.; Vehicle: Gum arabic suspension

ⓐ : Within 180 minutes

* : $P < 0.05$

Experiment 6 Acute toxicity in mice

(i) Method

Male Crj-ICR mice (4-weeks old, 21 ∿ 26 g) were used. The animals, divided into groups, each consisting of six mice, were administered orally with compound (1-12) at the dosage of 300 or 1000 mg/kg. Then, each group was housed in a cage, and observed for 24 hours. The test drugs were suspended in gum arabic, and administered at the volume of 0.1 ml/10 g.

(ii) Results

In both groups administered with compound (1-12) at the dosages of 300 and 1000 mg/kg, the state of sedation and ptosis were observed, but both were recovered within 3 hours. During 24-hour-observation, no test animals of either group were killed.

Reference Example 1

(1) L-Ascorbic acid acetonide (42 g, 0.19 mole) was dissolved in a solvent mixture of dimethylformamide (100 mℓ) and hexamethylphosphoramide (100 mℓ), and potassium carbonate (32 g, 0.23 mole) was added to the solution, followed by ice-cooling. A solution of chloromethyl methyl ether (18 g, 0.22 mole) in tetrahydrofuran (25 mℓ) was added dropwise to the mixture over the 20 minutes period. After stirring at room temperature for 2.5 hours, water (200 mℓ) was added to the reaction mixture, to which 2N hydrochloric acid was added to adjust to pH 5.0, followed by extraction with four portions of ethyl acetate. The organic layer was washed with water, dried and then concentrated under reduced pressure, and the residue was subjected to silica gel column chromatography, followed by elution with isopropyl ether - ethyl acetate (2:1). The eluate was concentrated, and the residue was recrystallized from the same solvent system to give L-5, 6-O,O-isopropylidene-3-O-methoxymethylascorbic acid (46 g). m.p. 93-94°C.

Elemental analysis, for $C_{11}H_{16}O_7$

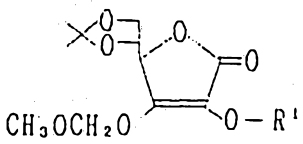
Found : C, 50.84; H, 6.05%

Calcd.: C, 50.77; H, 6.20

(2) L-5,6-O,O-Isopropylidene-3-O-methoxymethylascorbic acid (1.84 g, 7.1 mmole) was dissolved in dimethylsulfoxide (10 mℓ), and octadecyl iodide (2.68 g) and potassium carbonate (1.0 g) were added to the solution, followed by allowing the reaction to proceed at 60°C for 6 hours. After

the conclusion of the reaction, water (50 mℓ) was added to the reaction mixture, followed by extraction of the reaction product with ethyl acetate. The organic layer was washed with water, dried and concentrated under reduced pressure, and the residue was subjected to silica gel column chromatography, followed by elution with isopropyl ether. The eluate was concentrated, and the residue was recrystallized from isopropyl ether - ethyl acetate to give L-5,6-O,O-isopropylidene-3-O-methoxymethyl-2-O-octadecylascrobic acid (R 1-11) (0.8 g). The physico-chemical properties are shown in Table 6.

By the same procedure as in Reference Example 1, compounds shown in Table 6 [(R 1-1) to (R 1-33)] were prepared.



(5- and 6-positions form a isopropylidene)

Table 6

Compound	R' m.p.(℃)	NMR
R1-1	$-(CH_2)_5Me$ Oil	0.87(3H,m),1.25(8H,m),1.34(3H,s), 1.37(3H,s),3.50(3H,s),4.09(5H,m), 4.51(1H,d,2Hz),5.40(2H,s)
R1-2	$-(CH_2)_7Me$ Oil	0.85(3H,m),1.25(12H,s),1.34(3H,s), 1.37(3H,s),3.46(3H,s),4.12(5H,m), 4.56(1H,d,2Hz),5.46(2H,s)
R1-3	$-(CH_2)_8Me$ Oil	0.85(3H,m),1.27(14H,m),1.33(3H,s), 1.36(3H,s),3.48(3H,s),4.12(5H,m), 4.57(1H,d,2Hz),5.45(2H,s)
R1-4	$-(CH_2)_{10}Me$ Oil	0.87(3H,m),1.26(18H,m),1.33(3H,s), 1.37(3H,s),3.48(3H,s),4.12(5H,m), 4.56(1H,d,2Hz),5.46(2H,s)
R1-5	$-(CH_2)_{11}Me$ Oil	0.85(3H,m),1.25(20H,m),1.34(3H,s), 1.37(3H,s),3.47(3H,s),4.12(5H,m), 4.55(1H,d,2Hz),5.46(2H,s)
R1-6	$-(CH_2)_{12}Me$ Oil	0.86(3H,m),1.25(22H,m),1.34(3H,s), 1.37(3H,s),3.48(3H,s),4.13(5H,m), 4.56(1H,d,2Hz), 5.45(2H,s)

Table 6(continued)

Compound	R^1 m.p.(℃)	NMR
R1-7	$-(CH_2)_{13}Me$ Oil	0.86(3H,m),1.25(24H,m),1.33(3H,s), 1.37(3H,s),3.45(3H,s),4.12(5H,m), 4.56(1H,d,2Hz),5.46(2H,s)
R1-8	$-(CH_2)_{14}Me$ Oil	0.87(3H,m),1.24(26H,m),1.33(3H,m), 1.37(3H,s),3.49(3H,s),4.43(5H,m), 4.56(1H,d,2Hz),5.44(2H,s)
R1-9	$-(CH_2)_{15}Me$ 44-45	0.87(3H,m),1.25(28H,m),1.34(3H,s), 1.38(3H,s),3.50(3H,s),4.11(5H,m), 4.56(1H,d,2Hz),5.44(2H,s)
R1-10	$-(CH_2)_{16}Me$ Oil	0.85(3H,m),1.26(30H,m),1.33(3H,s), 1.36(3H,s),3.47(3H,s),4.11(5H,m), 4.57(1H,d,2Hz),5.47(2H,s)
R1-11	$-(CH_2)_{17}Me$ 50-52	0.85(3H,m),1.25(32H,m),1.33(3H,s), 1.37(3H,s),3.50(3H,m),4.12(5H,m), 4.57(1H,d,2Hz),5.47(2H,s)
R1-12	$-(CH_2)_{19}Me$ 57-58	0.85(3H,m),1.25(36H,m),1.33(3H,s), 1.36(3H,s),3.47(3H,s),4.25(5H,m), 4.57(1H,d,2Hz),5.43(3H,s)
R1-13	$-(CH_2)_{10}COOMe$ Oil	1.29(16H,m),2.30(2H,t,7Hz),3.51(3H, s),3.66(3H,s),4.11(3H,m),4.57(1H,d, 2Hz),5.45(2H,s)

Table 6 (continued)

Compound	R' properties	NMR
R1-14	$-(CH_2)_8OH$ Oil	1.30(20H,m),3.50(3H,s),3.51(3H,m),4.03(5H,m),4.51(1H,d,2Hz),5.58(2H,s)
R1-15	$-Bz$ Oil	1.34(3H,s),1.37(3H,s),3.38(3H,s),4.06(3H,m),4.50(1H,d,2Hz),5.05(2H,s),5.17(2H,s),7.20(5H,s)
R1-16	$-(CH_2)_3Ph$ Oil	1.31(3H,s),1.35(3H,s),1.97(2H,m),2.67(2H,m),3.42(3H,s),4.06(5H,m),4.50(1H,d,2Hz),5.36(2H,s),7.16(5H,m)
R1-17	4-Br-Bz Oil	1.34(3H,s),1.37(3H,s),3.46(3H,s),4.12(3H,m),4.58(1H,d,2Hz),5.09(2H,s),5.32(2H,s),7.31(2H,d,7Hz),7.50(2H,d,7Hz)
R1-18	4-Cl-Bz Oil	1.34(3H,s),1.38(3H,s),3.46(3H,s),4.14(3H,m),4.56(1H,d,2Hz),5.10(2H,s),5.31(2H,s),7.30(4H,s)
R1-19	4-Me-Bz Oil	1.34(3H,s),1.39(3H,s),2.33(3H,s),3.43(3H,s),4.10(3H,m),4.56(1H,d,2Hz),5.10(2H,s),5.26(2H,m),7.16(2H,d,8Hz),7.31(2H,d,8Hz)

Table 6(continued)

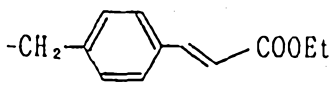
Compound	R' properties	NMR
RI-20	3-Me-Bz Oil	1.34(3H,s),1.38(3H,s),2.34(3H,s),3.43(3H,s),4.11(3H,m),4.54(1H,d,2Hz),5.24(2H,s),5.24(2H,m),7.20(4H,m)
RI-21	4-iPr-Bz Oil	1.23(6H,d,7Hz),2.90(1H,hep,7Hz),3.42(3H,s),4.12(3H,m),4.56(1H,d,2Hz),5.10(2H,s),5.25(2H,m),7.29(4H,m)
RI-22	4-COOMe-Bz Oil	1.33(3H,s),1.37(3H,s),3.46(3H,s),3.90(3H,s),4.12(3H,m),4.57(1H,d,2Hz),5.19(2H,s),5.32(2H,s),7.49(2H,d,8Hz),8.04(2H,d,8Hz)
RI-23	 Oil	1.32(3H,t,7Hz),1.33(3H,s),1.37(3H,s),3.44(3H,s),4.10(3H,m),4.23(2H,q,7Hz),4.57(1H,d,2Hz),5.14(2H,s),5.31(2H,s),6.42(1H,d,16Hz),7.47(4H,m),7.67(1H,d,16Hz)
RI-24	$-CH_2CH(Ph)_2$ Oil	1.32(6H,s),2.46(2H,m),3.44(3H,s),4.06(6H,m),4.53(1H,d,2Hz),5.36(2H,s),7.25(10H,s)
RI-25	$-(CH_2)_8OBz$ Oil	1.34(12H,m),1.37(6H,s),3.46(2H,t,7Hz),3.49(3H,s),4.09(5H,m),4.48(2H,s),4.54(1H,d,2Hz),5.42(2H,s),7.31(5H,s)

Table 6 (continued)

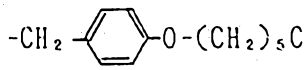
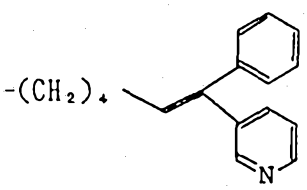
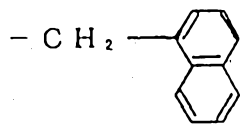
Compound	R' properties	NMR
R1-26	$-CH_2-$Cyclohexyl Oil	1.34(3H,s),1.38(3H,s),1.50(11H,m), 3.50(3H,s),4.12(5H,m),4.56(1H,d, 2Hz),5.43(2H,s)
R1-27	-Phenacyl Oil	1.33(3H,s),1.37(3H,s),3.53(3H,s), 4.11(3H,m),4.61(1H,d,2Hz),5.54(2H, m),5.74(2H,m),7.53(3H,m),7.91(2H,m)
R1-28	 Oil	0.88(3H,m),1.35(14H,m),3.40(3H,s), 3.91(3H,t,7Hz),4.08(3H,m),4.52(1H,d, 2Hz),5.01(2H,s),5.18(2H,s),6.80(2H, d,7Hz),7.27(2H,d,7Hz)
R1-29	 Oil	1.36(3H,s),1.38(3H,s),1.66(6H,m), 2.18(2H,m),3.48(3H,s),4.18(7H,m), 4.55(1H,m),5.40(2H,s),6.11(1H,t), 7.38(7H,m),8.42(1H,m),8.50(1H,m)
R1-30	 Oil	1.36(3H,s),1.44(3H,s),3.36(3H,s), 3.07(3H,m),4.51(1H,d),5.08(2H,s), 5.57(2H,s),7.45(7H,m)
R1-31	 Oil	0.88(3H,m),1.30(22H,m),1.36(3H,s), 1.37(3H,s),2.00(4H,m),3.51(3H,m), 4.10(5H,m),4.57(1H,d),5.31(2H,m), 5.42(2H,s)

Table 6 (continued)

Compound	R' properties	NMR
R1-32	$-CH_2COOMe$ Oil	1.37(6H,s),3.52(3H,s),3.74(3H,s), 4.12(3H,m),4.54(1H,d),4.75(2H,s), 5.49(1H,d),5.62(1H,d)
R1-33	$-(CH_2)_4COOMe$ Oil	1.37(6H,s),1.72(4H,m),2.35(2H,m), 3.49(3H,s),3.65(3H,s),4.10(5H,m), 5.36(2H,s)

Bz:benzyl, Me:methyl, Ph:phenyl, iPr:isopropyl, Et:ethyl

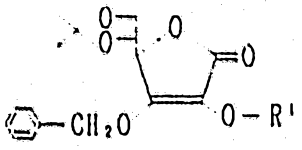
Reference Example 2

(1) L-ascorbic acid acetonide (21.6 g, 0.1 mole) was dissolved in dimethylformamide (120 mℓ), and the solution was cooled with ice. To the solution were added potassium carbonate (14 g, 0.1 mℓ) and successively benzyl bromide (11.2 mℓ), followed by stirring at room temperature for 20 hours. After the conclusion of the reaction, water (100 mℓ) was added to the reaction solution. To the mixture was added 2N hydrochloric acid to adjust to pH 5.0, followed by extraction with two portions of ethyl acetate. The organic layer was washed with water, dried (over magnesium sulfate) and then concentrated under reduced pressure. The product was subjected to silica gel column chromatography, and elution was effected with isopropyl ether - ethyl acetate (3:1). The eluate was concentrated, and then the residue was recrystallized from isopropyl ether - ethyl acetate to give L-5,6-O,O-isopropylidene-3-O-benzylascorbic acid (13 g, 40%), m.p. 105-106°C.

(2) L-5,6-O,O-isopropylidene-3-O-benzylascorbic acid (3.06 g, 0.01 mole) was dissolved in a solvent mixture of dimethyl-sulfoxide (20 mℓ) and tetrahydrofuran (15 mℓ), and potassium carbonate (1.5 g, 0.011 mole) was added to the solution. Then, octadecyl iodide (3.83 g) was added to the mixture, followed by stirring at room temperature for 18 hours. After the conclusion of the reaction, water (100 mℓ) was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with water,

dried (over magnesium sulfate) and then concentrated under reduced pressure. The residue was subjected to silica-gel column chromatography, followed by elution with isopropyl ether - ethyl acetate (10:1) to give L-5,6-O,O-isopropylidene-3-O-benzyl-2-O-octadecyl-ascorbic acid [compound (R2-7)] (3.8 g). The physico-chemical properties are shown in Table 7.

By the same procedure as in Reference Example 2, compounds shown in Table 7 [(R 2-1) to (R 2-12)] were prepared.

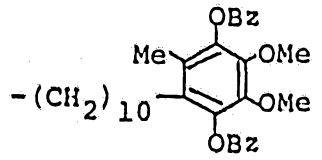
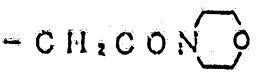
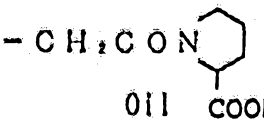


(5- and 6- positions form an isopropylidene)

Table 7

compound	R'	NMR
	m.p.(℃)	
R2-1	$-(CH_2)_7Me$	0.87(3H,m),1.27(12H,m),1.34(3H,s),
		1.37(3H,s),4.06,(5H,m),4.54(1H,d,
	Oil	2Hz),5.46(2H,s),7.36(5H,s)
R2-2	$-(CH_2)_8Me$	0.86(3H,m),1.26(16H,m),1.34(3H,s),
		1.37(3H,s),4.08(5H,m),4.54(1H,d,
	Oil	2Hz),5.46(2H,s),7.37(5H,s)
R2-3	$-(CH_2)_{15}Me$	0.86(3H,m),1.24(26H,m),1.34(3H,s),
		1.37(3H,s),4.08(5H,m),4.53(1H,d,
	Oil	2Hz),5.46(2H,s),7.36(5H,s)
R2-4	$-(CH_2)_{14}Me$	0.86(3H,m),1.26(26H,m),1.34(3H,s),
		1.37(3H,s),4.10(5H,m),4.53(1H,d,
	Oil	2Hz),5.46(2H,s),7.36(5H,s)
R2-5	$-(CH_2)_{15}Me$	0.85(3H,m),1.25(26H,m),1.34(3H,s),
		1.37(3H,s),4.06(5H,m),4.54(1H,d,
	Oil	2Hz),5.46(2H,s),7.37(5H,s)

Table 7 (continued)

Compound	R' m.p.(℃)	NMR
R2-6	$-(CH_2)_{10}Me$ Oil	0.87(3H,m),1.25(28H,m),1.34(3H,s), 1.37(3H,s),4.08(5H,m),4.54(1H,d, 2Hz),5.46(2H,s),7.36(5H,s)
R2-7	$-(CH_2)_{17}Me$ 44-45	0.88(3H,m),1.26(32H,m),1.38(6H,s), 4.08(5H,m),4.51(1H,d,2Hz),5.43(2H, s),7.29(5H,s)
R2-8	$-(CH_2)_{10}Me$ 48-50	0.87(3H,m),1.24(36H,m),1.34(3H,s), 1.37(3H,s),4.06(5H,m),4.54(1H,d, 2Hz),5.46(2H,s),7.36(5H,s)
R2-9	$-(CH_2)_{21}Me$ 60-61	0.87(3H,m),1.24(40H,m),1.34(3H,s), 1.37(3H,s),4.08(5H,m),4.53(1H,d, 2Hz),5.45(2H,s),7.36(5H,s)
R2-10	 Oil	1.26(16H,m),1.35(3H,s),1.37(3H,s), 2.14(3H,s),4.12(3H,m),4.51(1H,m), 4.81(2H,m),4.88(2H,s),4.95(2H,s), 7.30(15Hz),
R2-11	 Oil	1.37(6H,s),3.65(8H,m),4.10(3H,m), 4.55(2H,m),4.81(2H,m),5.67(2H,s), 7.30(5H,s)
R2-12	 Oil	1.32(3H,s),1.36(3H,s),2.04(3H,s), 3.60(3H,s),4.02(3H,m),4.23(3H,m), 4.53(3H,m),7.34(5H,m)

Reference Example 3

(1) L-5,6-O,O-Isopropylidene-3-O-benzyl-2-O-octadecyl-ascorbic acid (3.8 g) was dissolved in a solvent mixture of tetrahydrofuran (40 mℓ) and methanol (10 mℓ), and 2N hydrochloric acid (20 mℓ) was added to the solution, followed by stirring at 50°C for 24 hours. After the conclusion of the reaction, the reaction solution was concentrated under reduced pressure, and the reaction product was extracted with ethyl acetate. The organic layer was washed with water, dried and then concentrated under reduced pressure, and the residue was recrystallized from isopropyl ether - ethyl acetate to give 3-O-benzyl-2-O-octadecylascorbic acid [compound (R 3-7)] (2.6 g).

The physico-chemical properties are shown in Table 8.

(2) The compounds obtained in Reference Example 2 were processed by a procedure analogous to the above to prepare compounds [(R 3-1) to (R 3-12)], which are shown in Table 8.

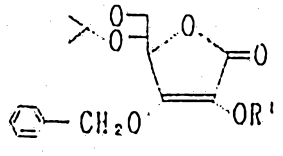
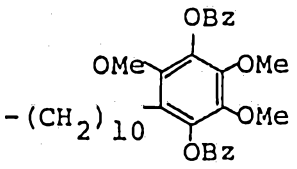
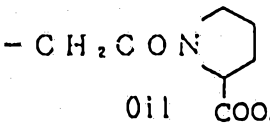


Table 8

Compound	R' m.p.(℃)	NMR
R3-1	$-(CH_2)_7Me$ Oil	0.87(3H,m),1.26(12H,m),4.00(5H,m), 4.66(1H,d,2Hz),5.45(2H,s),7.32(5H,s)
R3-2	$-(CH_2)_9Me$ Oil	0.86(3H,m),1.25(16H,m),3.80(2H,m), 4.00(3H,m),4.68(1H,d,2Hz),5.46(2H, s),7.36(5H,s)
R3-3	$-(CH_2)_{13}Me$ 65-66	0.86(3H,m),1.25(24H,m),3.80(2H,m), 4.00(3H,m),4.68(1H,d,2Hz),5.47(2H, s),7.35(5H,s),
R3-4	$-(CH_2)_{14}Me$ 62-63	0.87(3H,m),1.23(26H,m),3.82(2H,m), 4.02(3H,m),4.68(1H,d,2Hz),5.47(2H, s),7.36(5H,s)
R3-5	$-(CH_2)_{15}Me$ 71-72	0.86(3H,m),1.25(28H,m),3.85(2H,m), 4.02(3H,m);4.69(1H,d,2Hz),5.47(2H, 7.37(5H,s)

Table 8 (continued)

Compound	R¹ m.p.(℃)	NMR
R3-6	$-(CH_2)_{16}Me$ 57-58	0.88(3H,m),1.25(30H,m),3.79(2H,m), 4.00(3H,m),4.67(1H,d,2Hz,),5.44(2H, s),7.33(5H,s)
R3-7	$-(CH_2)_{17}Me$ 75-76	0.87(3H,m),1.25(32H,m),3.80(2H,m), 4.01(3H,m),4.68(1H,m),5.46(2H,s), 7.34(5H,s)
R3-8	$-(CH_2)_{18}Me$ 77-78	0.86(3H,m),1.24(36H,m),4.00(5H,m), 4.68(1H,m),5.46(2H,s),7.36(5H,s),
R3-9	$-(CH_2)_{21}Me$ 83-85	0.86(3H,m),1.25(40H,m),3.82(2H,m), 4.02(3H,m),4.69(1H,d,2Hz),5.46(2H, s),7.36(5H,s)
R3-10	 Oil	1.40(16H,m),2.13(3H,m),2.23(2H,m), 3.91(6H,s),4.06(5H,m),4.90(2H,s), 4.97(2H,m),5.57(2H,m),7.30(15H,m)
R3-11	 Oil	3.37(4H,m),3.49(4H,m),3.90(2H,m), 4.20(1H,m),4.79(2H,m),4.89(1H,d), 5.56(1H,d),5.75(1H,d),7.40(5H,s)
R3-12	 Oil	2.04(4H,m),3.49(2H,m),3.60(3H,s), 4.02(3H,m),4.23(1H,m),4.53(3H,m), 7.34(5H,s)

Reference Example 4

L-5,6-O,O-Isoprpylidene ascorbic acid (52g, 0.24 mole) was dissolved in a mixture of tetrahydrofuran (200 ml) and DMF(50 ml). Potassium carbonate (42 g, 0.3 mole) was added to the reaction mixture and the mixture was stirred for 10 minutes at room temperature. To the reaction mixture chloromethy ethyl ether (27 ml, 0.3 mole) was added during 5 minutes under keeping about 20°C in an ice bath. After stirring for 4 hours at room temperature, the reaction mixture was poured onto water (300 ml), adjusted at pH 8 by adding 2N hydrochloric acid and then extracted twice (400 ml, 200 ml) with ethyl acetate. The organic layer was washed with water, dried and concentrated under reduced pressure. The resulting crude product was purified with silica gel column chromatography (300 g, Merck Ltd. Art 7734, developing solvent; ethyl acetate: isopropyl ether = 1:2) and then recrystallized from isopropyl ether (crystallized out in refrigerator) to give 5,6-O,O-isopropylidene-3-O-ethoxymethyl-(L)-ascorbic acid (40 g, 61%).

Reference Example 5

L-5,6-O,O-Isopropylidene-3-O-ethoxymethyl ascorbic acid (13.6 g, 0.05 mole) and octadecyl iodide (20 g, 0.055 mole) were dissolved in a mixture of tetrahydrofuran (200 ml) and DMSO (50 ml), and added potassium carbonate (8 g, 0.06 mole) to the reaction mixture under stirring at room temperature. After stirring the mixture for

3 hours at 50°C, water (300 ml) was added to the mixture. The reaction mixture was adjusted to pH 7 with 2N hydrochloric acid and extracted with isopropyl ether (600 ml). The organic layer was washed with water, dried and concentrated under reduced pressure. The resulting crude product was purified with silica gel column chromatography (300 g, developing solvent; isopropyl ether) to give 5,6-O,O-isopropylidene-3-O-ethoxymethy-2-O-octedecyl-(L)-ascorbic acid (15 g, 57 %). This compound did not form any crystals at room temperature.

Reference Example 6

(1) To a solution of 2-O-octadecyl-L-ascorbic acid (0.8 g, 2 mmole) in chloroform (20 mℓ) was added pyridine (1 mℓ), followed by adding dropwise benzoyl chloride (0.28 g, 2 mmole) at room temperature. The reaction mixture was stirred for one hour, to which was added 2N hydrochloric acid to acidify it. The organic layer was washed with water and dried (over magnesium sulfate). The solvent was evaporated off, and the product was recrystallized from isopropyl ether - ethyl acetate to give 3-O-benzoyl-2-O-octadecyl-L-ascorbic acid (0.6 g, 49%), m.p. 68-69°C. $C_3H_{48}O_7$ (Found: C,69.94; H,8.98%. Anal. Calcd: C,69.89; H,9.08)

(2) By the same procedure as in the above, 2-O-hexadecyl-L-ascorbic acid was subjected to benzoylation to give 3-O-benzoyl-2-O-hexadecyl-L-ascorbic acid, m.p. 77-78°C. $C_{29}H_{44}O_7$ (Found: C,69.21; H,8.82%. Anal. Calcd.: C,69.02; H,8.79)

Example 1

L-5,6-O,O-Isopropylidene-3-O-methoxymethyl-2-O-octadecylascorbic acid (1.2 g) was dissolved in a solvent mixture of methanol (30 mℓ) and tetrahydrofuran (10 mℓ), and 2N hydrochloric acid (10 mℓ) was added to the solution, followed by stirring at 50°C for 6 hours. The reaction solution was concentrated under reduced pressure, and the reaction product was extracted with ethyl acetate. The organic layer was washed with water, dried (over magnesium sulfate) and then concentrated under reduced pressure, and the residue was recrystallized from isopropyl ether - ethyl acetate to give 2-O-octadecylascorbic acid [compound (1-12)] (0.82 g). This compound was also obtained from L-5,6-O,O-isopropylidene-3-O-ethoxymethyl ascorbic acid by hydrolysis mentioned above. The physico-chemical properties are shown in Table 9.

Example 2

3-O-Benzyl-2-O-octadecylascorbic acid (2.1 g) was dissolved in ethyl acetate (25 mℓ), and 5% Pd-C (0.5 g) was added to the solution to conduct catalytic reduction under atmospheric pressure. The catalyst was filtered out, and the filtrate was concentrated under reduced pressure. The reaction product was recrystallized from isopropyl ether - ethyl acetate to give 2-O-octadecylascorbic acid [compound (1-12)] (1.5 g).

The physico-chemical properties are shown in Table 9.

Example 3

Compounds [(1-1) to (1-38)] prepared by a procedure similar to the above Examples 1 and 2 are set forth in Table 9.

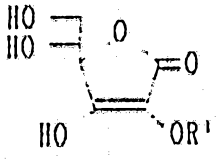


Table 9

Compound	R^1	Ex. No. depended	m.p. (℃)	NMR
1-1	$-(CH_2)_5Me$	1	100-101	0.88(3H,m),1.32(8H,m),3.54(2H,m),3.89(3H,m),4.70(1H,d,1Hz)
1-2	$-(CH_2)_7Me$	1,2	115-117	0.84(3H,m),1.26(12H,m),3.53(2H,m),3.85(3H,m),4.70(1H,d,1Hz)
1-3	$-(CH_2)_9Me$	1,2	122-123	0.86(3H,m),1.25(14H,m),3.54(2H,m),3.87(3H,m),4.71(1H,d,1Hz)
1-4	$-(CH_2)_8Me$	2	118-120	0.85(3H,m),1.24(16H,m),3.43(2H,m),3.86(3H,m),4.72(1H,d,1Hz)
1-5	$-(CH_2)_{10}Me$	1	124-125	0.86(3H,m),1.24(18H,m),3.50(2H,m),3.87(3H,m),4.71(1H,d,1Hz)
1-6	$-(CH_2)_{11}Me$	1	127-128	0.85(3H,m),1.24(20H,m),3.53(2H,m),3.91(3H,m),4.72(1H,d,1Hz)

Table 9 (continued)

Compound	R^1	Ex. No. depended	m.p. (℃)	NMR
1-7	$-(CH_2)_{12}Me$	1	129-130	0.85(3H,m),1.25(22H,m),3.52(2H,m),3.91(3H,m),4.72,(1H,d,1Hz)
1-8	$-(CH_2)_{13}Me$	1,2	126-127	0.85(3H,m),1.25(24H,m),3.51(2H,m),3.90(3H,m),4.74(1H,d,1Hz)
1-9	$-(CH_2)_{14}Me$	1,2	126-127	0.85(3H,m),1.26(26H,m),3.45(2H,m),3.86(3H,m),4.73(1H,d,1Hz)
1-10	$-(CH_2)_{15}Me$	1,2	128-129	0.86(3H,m),1.24(28H,m),3.59(2H,m),3.94(3H,m),4.75(1H,d,1Hz)
1-11	$-(CH_2)_{16}Me$	1,2	127-129	0.86(3H,m),1.27(30H,m),3.54(2H,m),3.86(3H,m),4.71(1H,d,1Hz)
1-12	$-(CH_2)_{17}Me$	1,2	127-128	0.85(3H,m),1.26(32H,m),3.51(2H,m),3.91(3H,m),4.75(1H,d,1Hz)
1-13	$-(CH_2)_{18}Me$	1,2	126-127	0.85(3H,m),1.23(36H,m),3.45(2H,m),3.86(3H,m),4.70(1H,d,1Hz)

Table 9 (continued)

Compound	R'	Ex. No. deperded	m.p. (℃)	NMR
1-14	$-(CH_2)_{21}Me$	1, 2	125-127	0.86(3H,m), 1.24(40H,m), 3.46(2H,m), 3.86(3H,m), 4.70(1H,s)
1-15	$-(CH_2)_{10}COOMe$	1	78- 79	1.26(16H,m), 2.26(2H,t, 7Hz), 3.45(2H,m), 3.54(3H,m), 4.73(1H,s)
1-16	$-(CH_2)_8OH$	1	73- 74	1.30(16H,m), 3.45(4H,m), 3.80(3H,m), 4.73(1H,s)
1-17	-Bz	1	126-127	3.44(2H,m), 3.78(1H,m), 4.74(1H,s), 4.96(2H,s) 7.38(5H,m)
1-18	$-(CH_2)_3Ph$	1	107-108	1.92(2H,m), 2.67(2H,m), 3.48(2H,m), 3.77(1H,m), 3.92(2H,t,7Hz), 4.77(1H, s), 7.23(5H,m)
1-19	4-Br-Bz	1	184-185	3.45(3H,m), 3.76(1H,m), 4.75(1H,s), 4.92(2H,s) 7.36(2H,d,8Hz), 7.54(2H, d,8Hz)
1-20	4-Cl-Bz	1	174-175	3.55(2H,m), 3.84(1H,m), 4.75(1H,s), 4.98(2H,s), 7.38(4H,m)

Table 8 (continued)

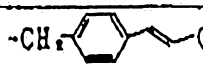
Compound	R^1	Ex. No. depended	m.p. (℃)	NMR
1-21	4-Me-Bz	1	157-158	2.28(3H,s),3.45(2H,m),3.75(1H,m),4.73(1H,s),4.90(2H,s),7.14(2H,d,7Hz),7.31(2H,7Hz)
1-22	3-Me-Bz	1	92-93	2.30(3H,s),3.44(2H,m),3.77(1H,m),4.75(1H,d,1Hz),4.92(2H,s),7.20(4H,m)
1-23	4-iPr-Bz	1	118-119	1.20(6H,d,7Hz),3.87(1H,hep,7Hz),3.45(2H,m),3.76(1H,m),4.73(1H,s),4.71(2H,s),7.27(4H,m)
1-24	4-COOMe-Bz	1	171-172	3.44(2H,m),3.75(2H,m),3.84(3H,s),4.74(1H,s)5.03(2H,s),7.55(2H,d,7Hz),7.95(2H,d,7Hz)
1-25		1	158-160	1.28(3H,t,7Hz),3.46(2H,m),3.81(1H,m),4.22(2H,q,7Hz),4.78(1H,s),5.22,(2H,s),6.22(1H,d,16Hz),7.49(2H,d,8Hz),7.62(1H,d,16Hz),7.72(2H,m)

Table 9 (continued)

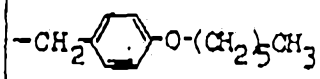
Compound	R^1	Ex. No. depended	m.p. (℃)	NMR
1-26	$-(CH_2)_2CH(Ph)_2$	1	129-130	2.37(2H,m),3.45(2H,m),3.78(3H,m),4.17(1H,t,7Hz),4.74(1H,d,1Hz),7.26(10H,m)
1-27	$-(CH_2)_6OCH_2Ph$	1	75- 76	1.29(12H,m),3.40(4H,m),3.87(3H,),4.42(2H,s),4.74(1H,s),7.29(5H,s)
1-28	$-CH_2$-Cyclohexyl	1	125-126	1.25(6H,m),1.83(7H,m),3.37(2H,m),3.62(3H,s),4.84(1H,s)
1-29	-Phenacyl	1	145-146	3.43(2H,m),3.78(1H,m),4.76(1H,s),5.33(2H,s)7.58(3H,m),7.89(2H,m)
1-30		1	133-134	0.88(3H,m),1.33(8H,m),3.45(2H,m),3.73(1H,m),3.93(2H,t,7Hz),4.72(1H,d,1Hz),4.86(2H,s),6.84(2H,d,8Hz),7.32(2H,d,8Hz)
1-31		2	Oil	3.56(11H,m),4.40(1H,m),4.56(2H,m),4.84(1H,d,2Hz)

Table 9 (continued)

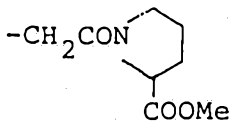
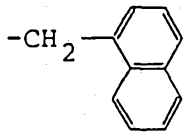
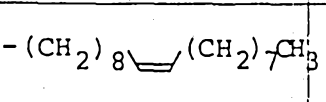
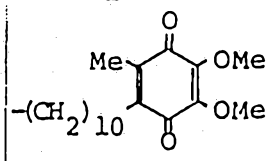
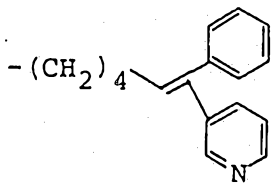
Compound	R¹	Ex. No. depended	m.p. (℃)	NMR
1-32		2	Oil	1.95(4H,m),3.44(5H,m),3.62(3H,s),4.35(1H,m),4.60(1H,m),4.74(1,d,2Hz)
1-33		1	Oil	3.66(5H,m),4.74(1H,d,2Hz),5.40(2H,m),7.45(7H,m)
1-34		1	101-104	0.86(3H,m),1.25(22H,m),1.98(4H,m),2.80(5H,m),4.69(1H,d,2Hz),5.21(2H,t,6Hz)
1-35	$-CH_2COOCH_3$	1	Oil	3.54(3H,m),3.65(3H,s),3.88(5H,m),4.67(1H,d,2Hz)
1-36	$-(CH_2)_4COOCH_3$	1	Oil	1.70(4H,m),2.35(2H,m),3.65(3H,s),3.88(5H,m),4.67(1H,d,2Hz)
1-37		2	Oil	1.28(16H,m),2.12(3H,s),2.57(2H,m),3.90(5H,m),3.85(6H,s)

Table 9 (continued)

Compound	R^1	Ex. No. depended	m.p. (℃)	NMR
1-38		1	Oil	1.46(6H,m),2.10(2H,m), 3.80(5H,m),4.63(1H,d, 2Hz),6.10(1H,t,7Hz), 7.38(7H,m),8.45(2H,m)

Incidentally, the compound (1-37) was obtained by subjecting a hydroquinone compound, prepared after conducting a procedure analogous to Example 2, to oxidation with ferric chloride.

Example 4

(1) To a solution of 2-octadecyl-L-ascorbic acid (0.8 g, 2 mmole) in chloroform (20 mℓ) were added pyridine (1 mℓ) and 4,4-dimethylaminopyridine (0.1 g), followed by adding acetyl chloride (0.25 mℓ) at room temperature. The reaction

solution was stirred for 18 hours, then the organic layer was washed with 2N hydrochloric acid, followed by washing with water and drying. The solvent was evaporated off under reduced pressure, and the product was recrystallized from isopropyl ether - ethyl acetate to give 6-O-acetyl-2-O-octadecyl-L-ascorbic acid (0.6 g, 65%), m.p. 117-118°C. $C_{26}H_{40}O_7$ (Found: C,66.24; H,9.95%. Anal. Calcd: C,66.35; H,9.85).

(2) By a procedure analogous to the above, 2-O-pentadecyl-L-ascorbic acid, 2-O-hexadecyl-L-ascorbic acid and 2-O-octadecyl-L-ascorbic acid were respectively subjected to acetylation, benzoylation, phenyl-acetylation and succinylation to give the following compounds.

(i) 6-O-Acetyl-2-O-pentadecyl-L-ascorbic acid, m.p. 112-113°C. $C_{23}H_{40}O_7$ (Found: C,64.59; H,9.48%. Anal. Calcd: C,64.46; H,9.41)

(ii) 6-O-Benzoyl-2-O-pentadecyl-L-ascorbic acid, m.p. 139-140°C. $C_{28}H_{42}O_7$ (Found: C,68.36; H,8.78%. Anal.Calcd: C,68.55; H,8.63)

(iii) 6-O-Phenylacetyl-2-O-pentadecyl-L-ascorbic acid, m.p. 126-127°C. $C_{29}H_{44}O_7$ (Found: C,68.79; H,8.99%. Anal. calcd: C,69.02; H,8.79)

(iv) 6-O-Acetyl-2-O-hexadecyl-L-ascorbic acid, m.p. 114-115°C. $C_{24}H_{42}O_7$ (Found: C,65.02; H,9.46%. Anal.Calcd: C,65.13; H,9.56)

(v) 6-O-Nicotynoyl-2-O-octadecyl-L-ascorbic acid hydrochloride, m.p. 142-143°C. $C_{34}H_{48}NO_7Cl$ (Found: C,66.49; H,8.70; N,2.20%. Anal. Calcd: C,66.06; H,7.83; N,2.27)

(vi) 6-O-(3-Carboxypropionyl)-2-O-tetradecyl-L-ascorbic acid, m.p. 155-156°C. $C_{24}H_{40}O_9$ (Found: 60.73; H, 8.66%. Anal. Calcd: C, 60.99; H, 8.53)

(vii) 6-O-(3-Carboxypropionyl)-2-O-pentadecyl-L-ascorbic acid, m.p. 156-157°C. $C_{25}H_{42}O_9$ (Found: 61.59; H, 8.87%. Anal. Calcd: C, 61.71; H, 8,70)

viii) 6-O-(3-Carboxypropionyl)-2-O-octadecyl-L-ascorbic acid, m.p. 155-156°C. $C_{28}H_{48}O_9$ (Found: 63.49; H,9.33%. Anal. Calcd: C, 63.61; H, 9.15)

Example 5

To a solution of 2-O-octadecyl-L-ascorbic acid (0.8 g, 2 mmole) in chloroform (20 mℓ) was added pyridine (1 mℓ). To the mixture was added dropwise acetyl chloride (0.25 mℓ) at room temperature. The reaction solution was stirred for one hour, followed by washing with 2N hydrochloric acid. The organic layer was washed with water and dried. The solvent was evaporated off under reduced pressure. The product was recrystallized from isopropyl ether - ethyl acetate to give 3-O-acetyl-2-O-actadecyl-L-ascorbic acid (0.8 g, 87%), m.p. 78-79°C. $C_{26}H_{46}O_7$ (Found: C,66.07; H,9.80%. Anal.Calcd: C,66.35; H,9.85)

Example 6

To a solution of 2-O-octadecyl-L-ascorbic acid (0.8 g, 2 mmole) and phenylisocyanate (0.24 g, 2 mmole) in chloroform (20 mℓ) was added trichloracetic acid (0.1 mℓ). The mixture was heated at 60°C for one hour, which was

washed with water, dried and concentrated to give a product. The product was recryslallized from isopropyl ether - ethyl acetate to give 6-O-phenylcarbamoyl-2-O-octadecyl-L-ascorbic acid (0.75 g), m.p. 149-150°C. $C_{31}H_{49}NO_7$ (Found: C,68.14; H,9.08; N,2.74%. Anal. Calcd: C,67.98; H,9.02; N,2.56).

Example 7

1) To a solution of sodium D-isoascorbate 120 g, 0.1 mole) in dimethylformamide (50 mℓ) was added dropwise benzyl bromide (12 mℓ). The mixture was heated at 50°C for 4 hours. To the reaction solution was added water (100 mℓ). The product was extracted with ethyl acetate. The organic layer was washed with water, dried and concentrated. Then, the crude product was subjected to silica-gel chromatography and developed with ethyl acetate to give 2-O-benzyl-D-isoascorbic acid (10 g, 37%). This benzyl compound(10 g, 0.037 mole) was dissolved in a mixture of dimethyl sulfoxide (40 mℓ) and tetrahydrofuran (10 mℓ). The solution was allowed to react with octadecyl iodide (14 g) in the presence of potassium carbonate (5 g) at 50°C for 2 hours. To the reaction product, after cooling, was added water (100 mℓ), and the product was extracted with isopropyl ether. The organic layer was washed with water, dried and concentrated under reduced pressure. The concentrate was subjected to silica-gel column chromatography, followed by development with isopropyl ether: ethyl acetate (1:1). Thus-obtained crude crystals were recrystallized from hexane: isopropyl ether (1:1) to give 2-O-octadecyl-3-

O-benzyl-D-isoascorbic acid (5 g, 26%), m.p. 62-63°C. $C_{31}H_{50}O_8$ (Found: C,72.02; H,9.67%. Anal.Calcd: C,71.78; H,9.72)

2) 2-O-Octadecyl-3-O-benzyl-D-isoascorbic acid obtained as above (3 g, 6.7 mmole) was dissolved in ethanol (50 mℓ). The solution was subjected to hydrogenation under atmospheric pressure in the presence of 5% Pd-carbon (0.2 g). Eighteen hours later, the catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The concentrate was recrystallized from ethyl acetate to give 2-O-octadecyl-D-isoascorbic acid (2 g, 80%), m.p. 103-104°C. $C_{24}H_{44}O_6$ (Found: C,67.45; H,10.46%. Anal.Calcd: C,67.26; H,10.35).

Example 8

To a solution of 5,6-O,O-isopropylidene-3-O-methoxymethyl-2-O-octadecyl-L-ascorbic acid (5 g, 10 mmole) in tetrahydrofuran (20 ml) was added 1,8-diazabicyclo[5,4,0]-7-undecene (3 mℓ). The mixture was stirred at 50°C for 2 hours. To the reaction mixture, after cooling, was added ethyl acetate (40 mℓ). The whole mixture was washed twice with 2N hydrochloric acid, followed by washing with water, drying and concentration under reduced pressure. The concentrate was stirred at 60°C for 6 hours in a mixture of ethanol (40 ml) and 2N hydrochloric acid (20 ml). The reaction solution was concentrated under reduced pressure, and the product was dissolved in ethyl acetate, washed with water, dried and concentrated. The crude product thus

obtained was recrystallized from isopropyl ether to give 2-O-octadecyl-5-dehydroxyascorbic acid (2 g, 51%), m.p. 114-115°C. $C_{24}H_{42}O_5$ (Found: C,70.24; H,10.42%. Anal. Calcd: C,70.21; H,10.31).

2-O-Octadecyl-5-dehydroxyascorbic acid obtained as above (0.4 g, 1 mmole) was dissolved in ethanol (10 mℓ). To the solution was added 5% Pd-carbon (0.2 g), and the mixture was stirred in hydrogen atmosphere for 4 hours under normal pressure. After completion of the reaction, the catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The concentrate was recrystallized from isopropyl ether - hexane to give the desired d,ℓ-2-O-octadecyl-5-deoxyascorbic acid (0.2 g), m.p. 83-84°C. $C_{24}H_{44}O_5$ (Found: C,69.33; H,10.74%. Anal. Calcd: C,69.86; H,10.75).

Example 9

By using the following ingredients, tablets are prepared by per se conventional means.

Compound (1-12) [Compound [I] wherein $R^1=(CH_2)_{17}CH_3$ $R^2=OH$, $R^3=H$]	50 mg
Corn starch	90 mg
Lactose	30 mg
Hydroxypropyl cellulose L	25 mg
Magnesium stearate	5 mg
Total (per tablet)	200 mg

Dosage is 1-3 tablets/adult after each meal (three times/day).

Example 10

By using the following ingredients, tablets are prepared by per se conventional means.

Compound (1-9) [Compound [I] wherein $R^1=(CH_2)_{14}CH_3$, $R^2=OH$, $R^3=H$]	60 mg
Corn starch	80 mg
Lactose	30 mg
Hydroxypropylcellulose L	25 mg
Magnesium stearate	5 mg
Total	200 mg

Dosage is 1-3 tablets/adult after each meal (three times/day).

Example 11

(1) To a solution of 2-O-octadecyl-L-ascorbic acid (0.8 g, 2 mmol) in acetone (50 mℓ) was added p-toluenesulfonic acid (50 mg). The mixture was stirred at room temperature for 6 hours. To the reaction solution was added sodium hydrogencarbonate (100 mg), which was then concentrated under reduced pressure. The resulting crude crystals were recrystallized from diisopropyl ether (IPE) to give 2-O-octadecyl-5,6-O,O-isopropylidene-L-ascorbic acid (0.8 g, 91%), m.p. 81-82°C.

(2) 2-O-Dodecyl-L-ascorbic acid and 2-O-hexadecyl-L-ascorbic acid were respectively subjected to a reaction analogous to the above to give the compounds shown below, respectively.

(i) 2-O-Dodecyl-5,6-O,O-isopropylidene-L-ascorbic acid, m.p. 83-84°C

(ii) 2-O-Hexadecyl-5,6-O,O-isopropylidene-L-ascorbic acid, m.p. 85-86°C

Example 12

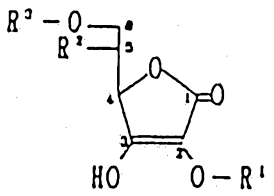
(1) To a solution of 2-O-hexadecyl-L-ascorbic acid (0.8 g, 2 mmol) and cyclohexanone (0.3 g) in toluene (50 mℓ) was added p-toluenesulfonic acid (50 mg). While the mixture was refluxed, the water then produced was separated. The reaction solution, after cooling, was washed with an aqueous solution of saturated sodium hydrogencarbonate, followed by drying and concentration under reduced pressure to give crude crystals, which were recrystallized from IPE to give 2-O-hexadecyl-5,6-O,O-cyclohexylidene-L-ascorbic acid (0.6 g, 84%), m.p. 80-81°C.

(2) 2-O-Dodecyl-L-ascorbic acid was subjected to a reaction analogous to the above to give the following compound.

(i) 2-O-Dodecyl-5,6-O,O-cyclohexylidene-L-ascorbic acid, m.p. 85-86°C.

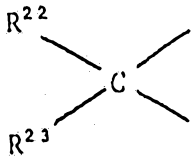
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of treating prophylaxis or for improving disorders in functions of the circulatory systems of mammals using a pharmaceutical composition containing an effective amount of an ascorbic acid derivative of the formula:



[I]

wherein R^1 is straight-chain or branched alkyl having 1 to 22 carbon atoms which may be substituted with a member selected from a group consisting of hydroxyl, carboxyl, aminocarbonyl, vinyl, ethynyl, cycloalkyl, aryl, morpholinyl, pyrrolidinyl, pyridyl, quinonylmethyl and chroman-2-yl; R^2 is hydrogen or hydroxyl; R^3 is hydrogen or acyl of C_{1-20} fatty acid, benzoic acid, thienylacetic acid or nicotinic acid which may be substituted with halogen C_{1-3} alkyl, C_{1-3} alkoxy or hydroxy, and R^3 and hydroxyl of R^2 may form



wherein R^{22} and R^{23} are independently hydrogen or C_{1-3} alkyl or R^{22} and R^{23} form $-(CH_2)_n-$ and n is 4 or 5, or a salt thereof, and a pharmaceutically acceptable carrier, vehicle or diluent therefor.

2. The method of claim 1, wherein R^1 is straight-chain alkyl having 9 to 20 carbon atoms.

3. The method of claim 1 or claim 2, wherein R^2 is hydroxyl.

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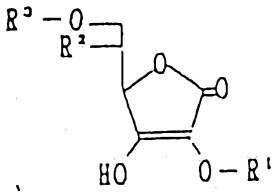
4. The method of any one of the preceding claims, wherein R^3 is hydrogen.

5. The method of claim 1, wherein the ascorbic acid derivative is 2-O-pentadecylascorbic acid.

6. The method of claim 1, wherein the ascorbic acid derivative is 2-O-octadecylascorbic acid.

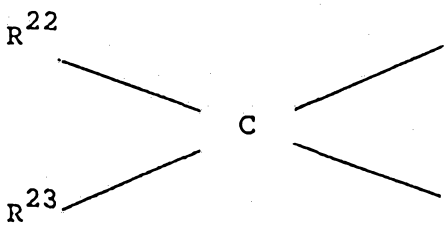
7. The method of any one of the preceding claims, wherein the composition is formulated to a tablet.

8. An ascorbic acid derivative of the formula:



[II]

wherein R^1 is: substituted benzyl substituted by C_{1-3} alkyl, C_{1-3} alkoxy, halogen, ethoxycarbonylethynyl, phenyl, carboxy, carboxy-methyl, 1-carboxyethyl or cyclohexyloxy; phenacyl; cycloalkylmethyl or C_{1-22} alkyl which is substituted with hydroxyl or benzyloxy; R^2 is hydrogen or hydroxyl; R^3 is hydrogen or acyl of C_{1-20} fatty acid, benzoic acid, thienylacetic acid or nicotinic acid which may be substituted with halogen C_{1-3} alkyl, C_{1-3} alkoxy or hydroxy, and R^3 and hydroxyl of R^2 may form



wherein R^{22} and R^{23} are independently hydrogen or C_{1-3} alkyl or R^{22} and R^{23} form $-(CH_2)_n-$ and n is 4 or 5, or a pharmaceutically acceptable salt thereof.

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9. The ascorbic acid derivative according to claim 8, wherein R^2 is hydroxyl.

10. The ascorbic acid derivative according to claim 8, wherein R^2 is hydrogen.

11. The ascorbic acid derivative according to claim 8, wherein R^3 is hydrogen.

12. The ascorbic acid derivative according to claim 8, wherein R^3 and hydroxyl of R^2 form ketal residue.

13. The ascorbic acid derivative according to claim 8, which is 2-O-(8-benzyloxyoctyl)-L-ascorbic acid.

14. The ascorbic acid derivative according to claim 8, which is 2-O-(4-hexyloxybenzyl)-L-ascorbic acid.

15. A method for treating prophylaxis or for improving disorders in functions of the circulatory systems of mammals as defined in claim 1 and substantially as herein described with reference to the accompanying Examples.

16. An ascorbic acid derivative as defined in claim 8 and substantially as herein described with reference to the accompanying Examples.

DATED 6th day of February 1990

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