1 589 525

PATENT SPECIFICATION

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(54) PROSTAGLANDINS AND PROCESS FOR THEIR MANUFACTURE

(71) We, HOECHST AKTIENGESELLSCHAFT, a body corporate organised according to the laws of the Federal Republic of Germany, of 6230 Frankfurt (Main) 80, Federal Republic of Germany, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

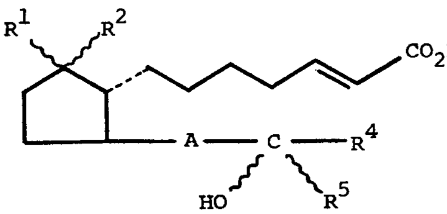
This invention relates to prostaglandins and to a process for their manufacture.

Prostaglandins are a group of fatty acids that are present in various tissues and organs of man and animals. The basic skeleton of the natural prostaglandins consists of 20 carbon atoms arranged in the form of a five-membered ring with a linear side chain on each of two adjacent carbon atoms.

The pharmacological effects of the prostaglandins are manifest *inter alia* in the fields of reproduction, blood pressure, gastroenterology, and in the bronchial muscle tonus. The pharmacological properties of the natural prostaglandins are the subject of numerous synopsis papers, for example, N. Andersen and P. W. Ramwell, Arch. Internal Med. *133*, 30 (1974); R. L. Jones, Pathobiology Ann. *1972*, 359; J. Pike, Scient. American *225*, 84 (1971), or M. P. L. Caton, Progress in Med. Chem., Vol 8, ed. Butterworth, London, 1971.

The synthesis of analogues of prostanoic acids which do not occur in nature and in which the great number of pharmacological actions of the natural prostaglandins is differentiated is of increasing importance.

The present invention provides a cyclopentane derivative of the general formula I



I

wherein

R¹ and R² together represent an oxygen atom or one represents a hydrogen atom and the other a hydroxyl group;

R³ represents a hydrogen atom or a linear or branched, saturated or unsaturated aliphatic or cycloaliphatic radical having up to 8 carbon atoms, or an araliphatic radical having from 7 to 9 carbon atoms;

R⁴ represents a linear or branched, saturated or unsaturated aliphatic hydrocarbon radical having up to 10 carbon atoms, or a cycloaliphatic radical having from 3 to 7 carbon atoms, each of the cited radicals optionally being substituted by any one or more of the following:

a) a linear or branched alkylthio or alkenylthio radical having up to 7 carbon atoms or, when R^5 is not a hydrogen atom and/or A is a —CH_2—CH_2— group and/or one of R^1 and R^2 represents a hydrogen atom and the other represents a hydroxyl group, a linear or branched alkoxy or alkenyloxy radical having up to 7 carbon atoms,

b) a phenoxy radical optionally mono- or di-substituted by one or two substituents selected from optionally halogen-substituted alkyl groups having from 1 to 3 carbon atoms, halogen atoms, optionally halogen-substituted phenoxy radicals and alkoxy radicals having from 1 to 4 carbon atoms; the substituents being identical or different in case of disubstitution,

c) a furyloxy, thienyloxy or benzyloxy radical, each of which is optionally mono- or disubstituted in the ring by one or two substituents selected from optionally halogen-substituted alkyl groups having from 1 to 3 carbon atoms, halogen atoms and alkoxy groups having from 1 to 4 carbon atoms, the substituents being identical or different in case of disubstitution;

d) one or two fluorine atoms, a trifluoromethyl or pentafluoroethyl group,

e) a cycloalkyl radical having from 3 to 7 carbon atoms,

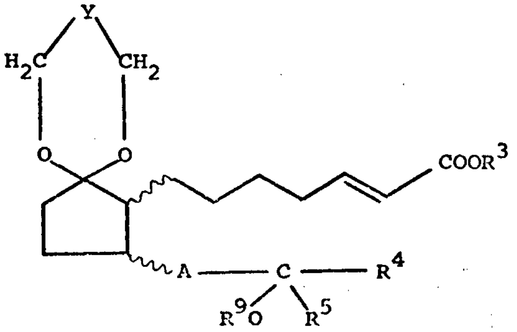
f) a phenyl, thienyl or furyl radical, each of which is optionally mono- or disubstituted by one or two substituents selected from optionally halogen-substituted alkyl groups having from 1 to 3 carbon atoms, halogen atoms and alkoxy groups having from 1 to 4 carbon atoms, the substituents being identical or different in case of disubstitution;

A represents a *trans* —CH=CH— group or a —CH_2—CH_2— group; and

R^5 represents a hydrogen atom, an alkyl group having from 1 to 5 carbon atoms, or an alkenyl or alkynyl group having from 2 to 5 carbon atoms with the proviso that when A represents a —CH_2—CH_2 group, R^5 is either a hydrogen atom or an alkyl group.

The invention also provides the salts of the compounds of the invention, especially the physiologically tolerable salts, for example, the alkali metal and alkaline earth metal salts, ammonium salts and substituted ammonium salts derived from primary, secondary or tertiary amines.

The present invention provides a process for the manufacture of a compound of the formula I or a salt thereof, which comprises removing by acidic hydrolysis the ketal protecting group from a compound of the formula XVII



XVII

wherein

R^3, R^4, R^5 and A are as defined for formula I, R^9 is a hydrogen atom or a protecting group which can be split off under acid conditions, and Y is a single bond, a CH_2 or a

$$-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-$$

group, R^5 represents only a hydrogen atom or an alkyl group having from 1 to 5 carbon atoms and, when R^9 does not represent a hydrogen atom, simultaneously or previously removing the protecting group R^9, and if desired, carrying out any one or more of the following steps, in any order,

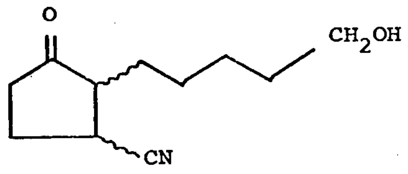
(i) esterifying the resulting compound of formula I wherein R^1 and R^2 together represent an oxygen atom, R^3 is a hydrogen atom and R^4, R^5 and A are as defined for formula I,

(ii) reducing a resulting compound of formula I wherein R^1 and R^2 together represent an oxygen atom and R^3, R^4, R^5 and A are as defined for formula I, to give a compound of formula I, wherein R^1 and R^2 are different, one representing a hydrogen atom and the other a hydroxyl group, and

(iii) converting a compound of formula I wherein R^3 is a hydrogen atom and R^1, R^2, R^4, R^5 and A are as defined for formula I, to a salt thereof.

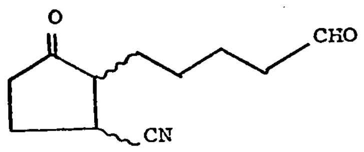
The compound of formula XVII is preferably prepared by a process which comprises

a) oxidizing an alcohol of the formula II



II

to form an aldehyde of the formula III

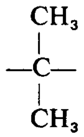


III

b) converting the aldehyde of formula III with a dithiol of the formula IV

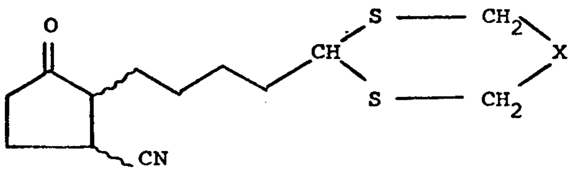
$HS—CH_2—X—CH_2—SH$ IV

wherein X is a single bond, a CH_2 group or a



$$-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}-$$

group, in the presence of an acidic catalyst, to a dithioacetal of the formula V



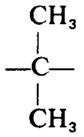
V

wherein X is as defined for formula IV,

c) reacting the dithioacetal of formula V with a diol of the formula VI

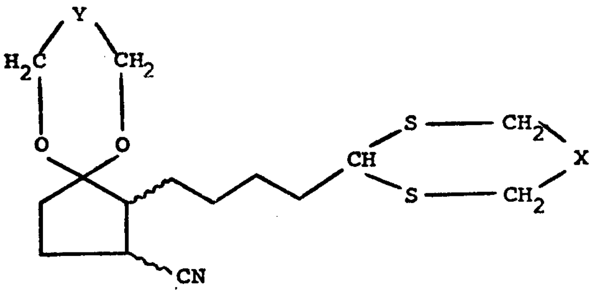
$HO—H_2C—Y—CH_2—OH$ VI

wherein Y is a single bond, a CH_2 group or a



$$-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}-$$

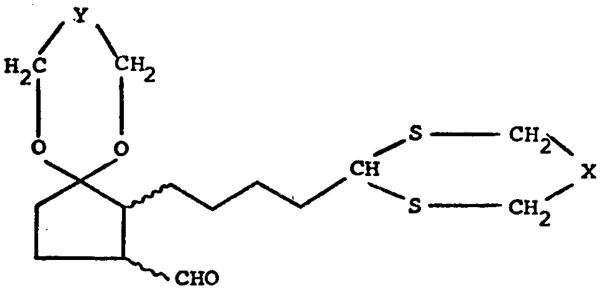
group, in the presence of an acidic catalyst, to form a ketal of the formula VII



VII

wherein X is as defined for formula IV and Y is as defined for formula VI,

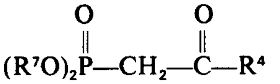
d) reducing the nitrile of formula VII to an aldehyde of the formula VIII



VIII

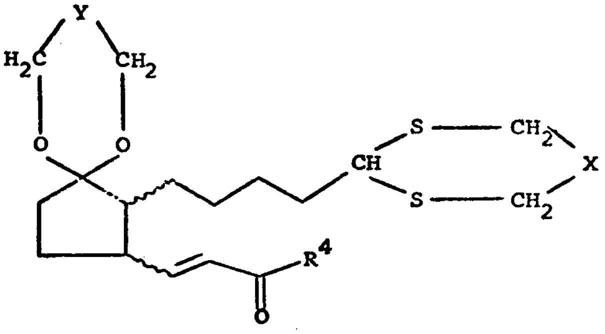
wherein X is as defined for formula IV and Y is as defined for formula VI,

e) reacting the aldehyde of formula VIII with a phosphonate of the formula IX



$$(R^7O)_2\overset{\overset{O}{\|}}{P}—CH_2—\overset{\overset{O}{\|}}{C}—R^4 \qquad \text{IX}$$

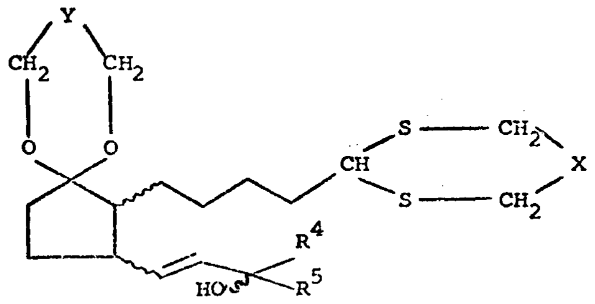
wherein R^4 is as defined for formula I, and R^7 is a linear alkyl radical having from 1 to 4 carbon atoms, to form an unsaturated ketone of the formula X



X

wherein X is as defined for formula IV and Y is as defined for formula VI,

f) reducing the unsaturated ketone of formula X to an alcohol of the formula XI



XI

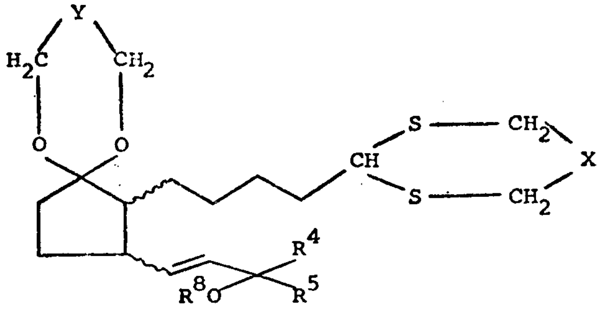
wherein R^4 is as defined for formula I, X is as defined for formula IV and Y is as defined for formula VI, and R^5 is a hydrogen atom, or

g) reacting the unsaturated ketone of formula X with an organometallic compound of the formula XII

$$R^5\text{—Me} \qquad \text{XII}$$

wherein R^5 represents an alkyl group having from 1 to 5 carbon atoms or alkenyl or alkynyl having from 2 to 5 carbon atoms and Me is an alkali metal or HalMg, (Hal being chlorine, bromine or iodine) to form a compound of formula XI, wherein R^4 is as defined for formula I, R^5 is as defined for formula XII, X is as defined for formula IV and Y is as defined for formula VI.

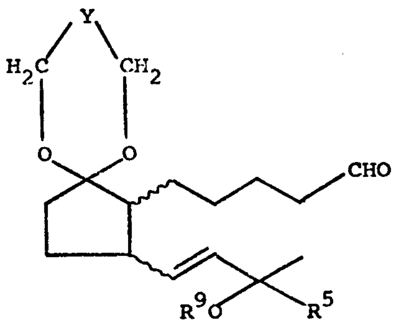
h) protecting the hydroxy group of the compound of formula XI by means of a group which can be split off under acidic conditions, thus forming a compound of the formula XIII



XIII

wherein R^4 and R^5 are as defined for formula I, X is as defined for formula IV, Y is as defined for formula VI, and R^8 is a protecting group which can be split off under acidic conditions,

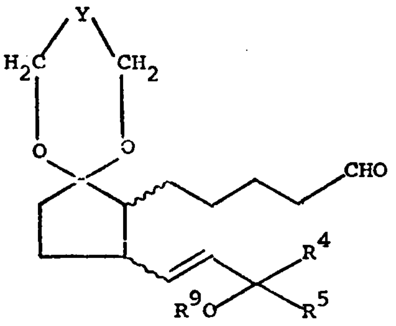
j) splitting off the thioacetal group of the compound of formula XI or XIII in a mixture of an organic solvent and water in the presence of a salt of a heavy metal or an alkyl halide, thus forming an aldehyde of the formula XIV



XIV

wherein R^4 and R^5 are as defined for formula I, Y is as defined for formula VI, and R^9 is hydrogen or a protecting group which can be split off under acidic conditions.

j') optionally hydrogenating the aldehyde of formula XIV so obtained to a compound of the formula XV



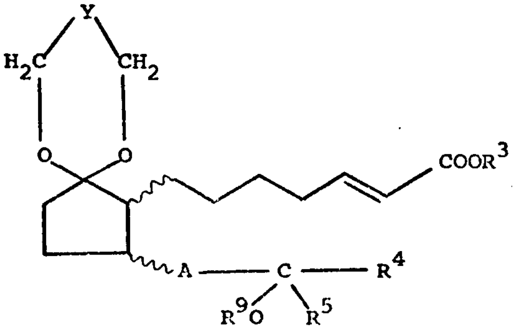
XV

wherein R^4 is as defined for formula I, R^9 is as defined for formula XIV, Y is as defined for formula VI and R^5 is a hydrogen atom or an alkyl group having from 1 to 5 carbon atoms, in the presence of a suitable catalyst,

k) reacting a compound of formulae XIV or XV, with an ylide of the formula XVI

$$(R^{10})_3P{=}CH{-}CO_2R^3 \qquad \text{XVI}$$

wherein the radicals R^{10} which may be identical or different, each represents a linear alkyl group having from 1 to 4 carbon atoms or a phenyl group, and R^3 is as defined for formula I, to form a compound of the formula XVII



XVII

wherein R^3, R^4, R^5 and A are as defined for formula I, R^9 is as defined for formula XV and Y is as defined for formula VI,

l) optionally preparing a compound of the formula XVII wherein R^9 is hydrogen, from the corresponding compound of formula XVII wherein R^9 is a protecting group which can be split off under acidic conditions, by means of mild acidic hydrolysis, and, to produce a compound I,

m) removing the ketal protecting group from the compound of formula XVII by means of acidic hydrolysis and when R^9 is not hydrogen, simultaneously or previously also the protecting group R^9, thus obtaining a compound of formula I, wherein R^1 and R^2 together are oxygen and R^3, R^4, R^5 and A are as defined for formula I and, if desired, carrying out any one or more of the following steps, in any order,

n) esterifying a compound of formula I, wherein R^1 and R^2 together are oxygen, R^3 is hydrogen and R^4, R^5 and A are as defined for formula I, to form a compound of formula I, wherein R^1 and R^2 together are oxygen, R^3 is a linear, branched, saturated or unsaturated aliphatic or cycloaliphatic radical having from 1 to 8 carbon atoms or an araliphatic radical having from 7 to 9 carbon atoms, and R^4, R^5 and A are as defined for formula I, and optionally

o) reducing a compound of formula I, wherein R^1 and R^2 together are oxygen, and R^3, R^4, R^5 and A are as defined for formula I, to a compound of formula I, wherein R^1 and R^2 are different and each are hydrogen or a hydroxyl group, and R^3, R^4, R^5 and A are as defined for formula I, and, if desired,

p) converting a compound of formula I, wherein R^3 is hydrogen and R^1, R^2, R^4, R^5 and A are as defined for formula I, into a salt, especially a physiologically tolerable metal or amine salt.

The symbols R^3, R^4 and R^5 preferably have the following meanings:

R^3: a hydrogen atom, a linear or branched alkyl radical having from 1 to 8 carbon atoms, a linear or branched alkenyl radical having from 2 to 4 carbon atoms, a cycloalkyl radical having from 5 to 7 carbon atoms, an aralkyl radical having 7 or 8 carbon atoms, or a physiologically tolerable metal, NH_4, or substituted ammonium ion derived from a primary, secondary or tertiary amine.

R^4: a linear or branched, saturated or unsaturated aliphatic hydrocarbon radical having from 1 to 8 carbon atoms, or a cycloaliphatic hydrocarbon radical having from 5 to 7 carbon atoms, each of the cited radicals optionally being substituted by

a) a linear or branched alkoxy, alkylthio, alkenyloxy or alkenylthio radical having from 1 to 5 carbon atoms (subject to the above proviso),

b) a phenoxy radical optionally mono- or disubstituted by one or two substituents selected from alkyl groups having from 1 to 3 carbon atoms, trifluoromethyl groups, halogen atoms, optionally halogen-substituted phenoxy radicals, methoxy and ethoxy radicals, the substituents being identical or different in case of disubstitution,

c) a thienyloxy or benzyloxy radical optionally mono- or disubstituted in the ring by one or two substituents selected from alkyl groups having from 1 to 3 carbon atoms, trifluoromethyl groups, halogen atoms, methoxy and ethoxy groups, the substituents being identical or different in case of disubstitution,

d) one or two fluorine atoms or a trifluoromethyl group,

e) a cycloalkyl radical having from 5 to 7 carbon atoms,

f) a phenyl or thienyl radical optionally mono- or disubstituted by one or two substituents selected from alkyl radicals having from 1 to 3 carbon atoms, a trifluoromethyl groups, halogen atoms, methoxy and ethoxy groups, the substituents being identical or different in case of disubstitution.

R^5: an alkyl group having from 1 to 5 carbon atoms, alkenyl or alkynyl group having from 2 to 4 carbon atoms.

The following meanings for the symbols R^3, R^4 and R^5 are especially preferred:

R^3: a hydrogen atom, a linear alkyl radical having from 1 to 6 carbon atoms, a branched alkyl radical having from 3 to 5 carbon atoms, a linear alkenyl radical having from 2 to 4 carbon atoms, a cyclopentyl, cyclohexyl, benzyl, phenethyl or methylbenzyl radical, or a physiologically tolerable metal, ammonium or substituted ammonium ion derived from a primary, secondary or tertiary amine.

R^4: a linear or branched alkyl radical having from 1 to 6 carbon atoms, a linear or branched alkenyl radical having from 3 to 5 carbon atoms, or a cycloalkyl radical having from 5 to 7 carbon atoms, each of the cited radicals optionally being substituted by

a) a linear or branched alkoxy, alkylthio, alkenyloxy, or alkenylthio radical having from 1 to 4 carbon atoms (subject to the above proviso),

b) a phenoxy radical optionally mono- or disubstituted by one or two substituents selected from methyl, trifluoromethyl and methoxy groups, chlorine and fluorine atoms, and a phenoxy radical optionally substituted by one or more chlorine and/or fluorine atoms, the substituents being identical or different in case of disubstitution,

c) a thienyloxy or benzyloxy radical optionally mono- or disubstituted in the ring by one or two substituents selected from methyl, trifluoromethyl and methoxy groups, the substituents being identical or different in case of disubstitution,

d) one or two fluorine atoms or a trifluoromethyl group,

e) a cycloalkyl radical having from 5 to 7 carbon atoms,

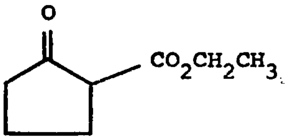
f) a phenyl or thienyl radical optionally mono- or disubstituted by one or two substituents selected from methyl, trifluoromethyl and methoxy groups, and chlorine and fluorine atoms, the substituents being identical or different in case of disubstitution.

Particularly preferred radicals R^4 are the following:
2,2 - dimethylhexyl, 3,3 - dimethylhexyl,4,4 - dimethylhexyl, 3 - ethyl - pentyl, 1,1 - dimethyl - 4 - pentenyl, 5 - methyl - 4 - hexenyl, 1 - methyl - 5 - cyclohexylpentyl, 5,5,5 - trifluoropentyl, 5 - trifluoromethylheptyl, 1,1 -

dimethyl - 7,7,7 - trifluoroheptyl, 1 - methyl - 6,6,6 - trifluoromethylhexyl, 1,1 - difluoro - 4,4 - dimethylpentyl, 4,4 - difluorocyclohexyl, 4 - trifluoromethyl - cyclohexyl, 3 - trifluoromethylcyclohexyl, 2 - trifluoromethyl - cycloheptyl, 3 - trifluoromethylcyclopentyl, 3,3 - dimethyl - 2 - oxapentyl, 3 - methyl - 2 - oxahexyl, 4,4 - dimethyl - 2 - oxapentyl, 1,1,4 - trimethyl - 2 - oxapentyl, 3,4 - dimethyl - 2 - oxapentyl, 5 - methyl - 2 - oxa - 4 - hexenyl, 2,2 - dimethyl - 3 - oxaheptyl, 1,1 - dimethyl - 3 - oxahexyl, 1,1 - dimethyl - 3 - oxaoctyl, 1,1,5,5 - tetramethyl - 3 - oxahexyl, 1 - methyl - 3 - oxahexyl, 1 - methyl - 3 - oxaoctyl, 1,1,6 - trimethyl - 3 - oxa - 5 - heptenyl, 1,1,6 - trimethyl - 3 - oxaheptyl, 7 - methyl - 4 - oxaoctyl, 1,1 - dimethyl - 4 - oxa - 6 - heptenyl, 4 - methoxycyclohexyl, 3 - butoxycyclohexyl, 2 - ethoxycyclohexyl, 3 - ethoxycyclopentyl, 4 - methoxycycloheptyl, 2 - thiapentyl, 2 - thiahexyl, 2 - thiaheptyl, 4,4 - dimethyl - 2 - thiapentyl, 5 - methyl - 2 - thia - 4 - hexenyl, 3 - thia - pentyl, 3 - thiahexyl, 5,5 - dimethyl - 3 - thiahexyl, 1,1 - dimethyl - 3 - thiapentyl, 1,1 - dimethyl - 4 - thiapentyl, 4 - chlorophenoxymethyl, 2 - chlorophenoxymethyl, 2,3 - dichlorophenoxymethyl, 2,4 - dichlorophenoxymethyl, 2,5 - dichlorophenoxymethyl, 2,6 - dichlorophenoxymethyl, 3,4 - dichlorophenoxymethyl, 3,5 - dichlorophenoxymethyl, 2 - chloro - 6 - methylphenoxymethyl, 2 - chloro - 4 - methylphenoxymethyl, 3 - chloro - 2 - methylphenoxymethyl, 4 - chloro - 2 - methylphenoxymethyl, 5 - chloro - 2 - methylphenoxymethyl, 4 - trifluoromethylphenoxymethyl, 2 - trifluoromethylphenoxymethyl, 2 - methyl - 5 - trifluoromethyl - phenoxymethyl, 3 - methyl - 5 - trifluoromethylphenoxymethyl, 3 - fluorophenoxymethyl, 2 - fluorophenoxymethyl, 2 - fluoro - 4 - trifluoromethylphenoxymethyl, 3,4 - difluorophenoxymethyl, 4 - fluoro - 2 - methylphenoxymethyl, 4 - phenoxyphenoxymethyl, 3 - *p* - chlorophenoxyphenoxymethyl, 4 - methoxyphenoxymethyl, 3 - methoxyphenoxymethyl, 4 - chloro - 3 - methoxyphenoxymethyl, 3 - chloro - 4 - methoxyphenoxymethyl, 4 - methoxy - 3 - methylphenoxymethyl, 4 - methoxy - 2 - methylphenoxymethyl, 3 - methoxy - 5 - methylphenoxy - methyl, 2 - (3 - chlorophenoxy)ethyl, 2 - (4 - chlorophenoxy)ethyl, 2 - (3 - trifluoromethylphenoxy)ethyl, 2 - (4 - methoxyphenoxy)ethyl, 2 - (3 - methylphenoxy)ethyl, 2 - (4 - fluorophenoxy)ethyl, 2 - (3 - chloro - 5 - methylphenoxy)ethyl, 1 - (3 - trifluoromethylphenoxymethyl)ethyl, 1 - (3 - chloro - phenoxymethyl)ethyl, 1 - (4 - fluorophenoxymethyl)ethyl, 1 - (4 - chloro - 3 - methylphenoxymethyl)ethyl, 1 - (3 - chloro - 4 - methoxyphenoxymethyl)ethyl, 1 - (3 - trifluoromethylphenoxymethyl) - 1 - methylethyl, 1 - (3 - chlorophenoxymethoxy) - 1 - methylethyl, 1 - (4 - fluorophenoxymethyl) - 1 - methylethyl, 1 - (3,4 - dichlorophenoxymethyl - 1 - methylethyl, 1 - (3 - chloro - 4 - methylphenoxy) - 2 - methylpropyl, 1 - (3 - chloro - 4 - phenoxyphenoxy) - 2 - methylpropyl, 1,1 - dimethyl - 4 - phenoxybutyl, 1,1 - dimethyl - 4 - (3 - trifluoromethylphenoxy) - butyl, benzyloxymethyl, 3 - chlorobenzyloxymethyl, 3 - trifluoromethyl - benzyloxymethyl, 4 - methoxybenzyloxymethyl, 3 - phenoxybenzyloxymethyl, 2 - methylbenzyloxymethyl, 4 - chloro - 3 - methoxybenzyloxymethyl, 3 - methoxy - 5 - methylbenzyloxymethyl, 1 - (3 - chlorobenzyloxymethyl) - 1 - methylethyl, 1 - (4 - trifluoromethylbenzyl - oxymethyl)ethyl, 3 - (4 - fluorobenzyloxy)propyl, 4 - (3 - chlorophenoxy) - cyclohexyl, 4 - (3 - trifluoromethylphenoxy) - cyclohexyl, 2 - phenoxycyclohexyl, 4 - (2 - chlorobenzyloxy) - cyclohexyl, benzyl, 3 - trifluoromethylbenzyl, 4 - methylbenzyl, 3 - chlorophenethyl, 4 - fluorophenethyl, 1 - benzyl - 1 - methylethyl, 1,1 - dimethyl - 4 - pentyl, 2 - methyl - 3 - thienyloxymethyl, 2 - chloro - 3 - thienyloxy - methyl, 2 - chloro - 4 - thienyloxymethyl, 3 - chloro - 4 - thienyloxymethyl, 2,5 - dimethyl - 3 - thienyloxymethyl, 2 - chloro - 3 - methyl - 4 - thienyloxymethyl, 2 - thienyloxymethyl, 4 - methyl - 2 - thienyloxymethyl, 5 - chloro - 2 - thienyloxymethyl, 5 - chloro - 3 - methyl - 2 - thienyloxymethyl, 5 - chloro - 3 - methyl - 2 - thienyloxymethyl, 3,5 - dimethyl - 2 - thienyloxymethyl, 1 - (3 - thenyl) - 1 - methylethyl, 3 - (3 - thienyl) - 1 - methylpropyl, 3 - (2 - methoxy - 4 - thienylpropyl, 3 - thenyl, 2 - chloro - 4 - thenyl, 2 - methyl - 5 - thenyl, 1,1 - dimethyl - 3 - (3 - thienypropyl, 2 - (4 - methoxy - 2 - thienyl) - ethyl.

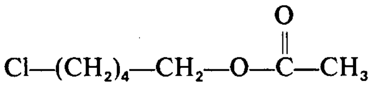
The 2(1 - hydroxypentyl) - 3 - oxo - cyclopentylnitrile of formula II used as starting material in the process of the invention may be prepared according to various processes for example, the following:

A 2 - oxocyclopentancarboxylic acid ethyl ester of formula XVIII



XVIII

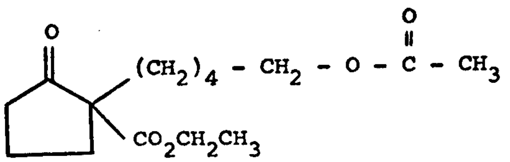
is reacted with a 5 - acetoxypentyl chloride of formula XIX



XIX

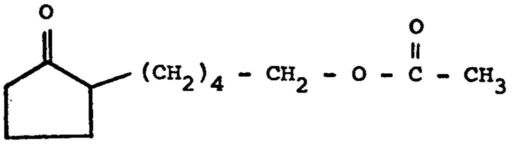
$$Cl-(CH_2)_4-CH_2-O-\overset{\overset{\displaystyle O}{\|}}{C}-CH_3$$

to form the 1-substituted - 2 - oxocylopentanecarboxylic acid ethyl ester of the formula XX



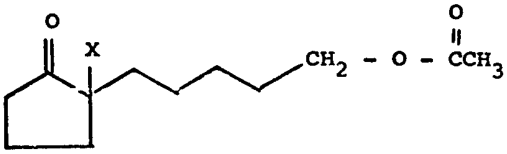
XX

which is decarboxylated by means of glacial acetic acid/H_2SO_4 to form the compound XXI

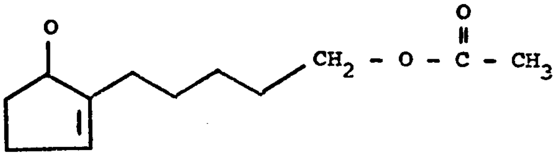


XXI

which is treated according to the process of German Offenlegungsschrift No. 2,430,700 in order to obtain the compound II via the compounds XXII and XXIII



X = Halogen XXII



XXIII

The process of the invention begins by oxidizing the alcohol of formula II to the aldehyde of formula III.

The oxidation of II to III may be carried out by means of any of the oxidation agents used for the oxidation of aliphatic alcohols to aldehydes. Some of these methods are indicated, for example, in Houben-Weyl, Methoden der Organischen Chemie, Vol. 7/1 Stuttgart 1954, p. 159 sqq.

Further suitable oxidation agents are the complex formed from thioanisole and chlorine (J. Org. Chem. *38*, 1233 (1973)), the chromium trioxide/pyridine complex (J. Org. Chem. *35*, 4000 (1970) and J. Org Chem. *26*, 4814 (1961)), and dimethyl sulfoxide with different coreactants (J. Amer. Soc. *87*, 5661 (1965), *88*, 1762 (1966), *89*, 5505 (1967): Chem. Rev. *67*, 247 (1967)).

A particularly preferred process is oxidation by means of the complex formed from dimethyl sulfoxide and N-chlorosuccinimide, substantially according to the indications of J. Amer. Chem. Soc. *94*, 7586 (1972).

The aldehyde of formula III may then be purified by distillation or chromatography; however, it is advantageous to react it directly and selectively in crude form with the dithiol of formula IV in an inert solvent and in the presence of an acidic catalyst to form the dithioacetyl of formula V.

The compound III and the dithiol IV are preferably used in about stoichiometric amounts, the reaction generally being carried out at a temperature of from +10 to −30°C.

Preferably the crude aldehyde III is reacted with a small excess of the dithiol of formula IV in benzene or methylene chloride at a temperature of from −5 to +10°C and in the presence of boron trifluoride etherate and optionally a dehydrating agent, for example, magnesium sulfate.

The dithioacetal V so obtained may then be purified by distillation or chromatography, or may be reacted directly with a diol of formula VI in an inert solvent, for example, benzene or toluene, in the presence of an acidic catalyst and optionally in the presence of a dehydrating agent to form the ketals of formula VII. Preferably the dithioacetal V is refluxed in benzene or toluene in a water separator and in the presence of an acidic catalyst, for example, *p*-toluenesulfonic acid, and an amount of a diol VI slightly above the theoretical quantity and the resulting compound VII is subsequently worked up in usual manner.

The ketal of formula VII may be purified by distillation under highly reduced pressure or by chromatography, and subsequently the cyano group can be reduced in known manner to give an aldehyde group *i.e.* to give the compound of formula VIII. For this step, there may be used any reducing agent suitable for the reduction of a nitrile group to an aldehyde group, preferably a complex metal hydride, for example, lithiumtriethoxyaluminium hydride Particularly preferred is diisobutylaluminium hydride in an inert solvent, for example, an aliphatic or aromatic hydrocarbon or anhydrous ether, for example, diethyl ether, tetrahydrofuran or 1,2 - dimethoxyethane. The reduction is generally carried out at a temperature of from −40 to +40°C, preferably from −10 to +10°C.

The reduction of the compound VII is preferably as follows: an equimolar amount of a slight excess of diisobutylaluminium hydride is added dropwise to a solution of VII in toluene at a temperature of from −5 to +5°C. After two to three hours, the reduction is generally complete, and the aldimine may be hydrolyzed by adding glacial acetic acid and water to form the aldehyde VIII, which may be used directly for the next process step without special purification or, optionally, may be purified by column chromatography.

The reaction of the phosphonate of formula IX with the compound of formula VIII may be carried out under the conditions usual for the Horner reaction, for example, in an ether at room temperature. Preferred ethers are diethyl ether, tetrahydrofuran and 1,2 - dimethoxyethane. To ensure completion of the reaction, the phosphonate is employed in excess. Generally, the reaction is complete after 3 to 24 hours at a temperature of from 20 to 50°C. The reaction product of formula X may then be isolated from the reaction mixture and purified according to known methods. This reaction is described in J. Amer. Chem. Soc. *83*, 1733 (1961).

The phosphonates of formula IX are either known (J. Org. Chem. 30, 680 (1965)), or they may be prepared in analogy to known processes (for example J. Amer. Chem. Soc. *88*, 5654 (1966)).

A compound of formula XI (R^5=H) can be obtained by treating the compound of formula X with a reducing agent. There may be used any reducing agent which allows the selective reduction of a carbanyl group to a hydroxyl group in the presence of an olefinic double bond. Preferred reducing agents are complex metal hydrides, especially borohydrides, for example, potassium or sodium borohydride, zinc borohydride or lithiumperhydro - 9b - boraphenalyl hydride (J. Amer. Chem. Soc. *92*, 709 (1970)), and aluminium hydrides, for example, sodiumbis - (2 - methoxethoxy) - aluminium hydride or diisobutylaluminium hydride. Generally, the reduction is carried out at a temperature of from −10 to 50°C in a solvent inert to the hydride, for example an ether, for example diethyl ether, 1,2 - dimethoxyethane, dioxane, tetrahydrofuran or diethyleneglycoldimethyl ether, or a hydrocarbon, for example, benzene, or in an alcohol/water mixture, for example, ethanol/water.

To prepare an alkylated compound of formula XI (R^5=alkyl, alkenyl or alkynyl), the ketone of formula X is reacted with an organometallic compound of formula XII, for example, an organolithium or organo-magnesium (Grignard) compound.

The reaction is generally carried out in a solvent inert under the reaction conditions, for example, in a hydrocarbon or, preferably, an ether, for example, diethyl ether, THF or 1,2 - di - methoxyethane. The temperatures may be from

−60 to +30°C, preferably from −30 to −10°C. The isomeric α- and β-hydroxy compounds XI obtained in the reduction or the organo-metallic reaction can be separated to yield the two isomers by means of usual chromatographic methods. The subsequent reactions may alternatively be carried out using a mixture of both the isomers, with separation of the resulting isomers to give α- and β-hydroxy compounds in any step following the reduction.

The hydroxyl group in the compound of formula XI may be protected by means of any protecting group which can be easily split off, especially those groups which are introduced by acidic catalysis, mainly by reaction with an enol ether. Especially suitable enol ethers are 2,3 - dihydropyran, ethylvinyl ether and methyl isopropenyl ether; suitable acidic catalysts are, for example, *p*-toluenesulfonic acid and sulfuric acid. The reaction is advantageously carried out in an aprotic solvent, for example, diethyl ether, dioxane or benzene, the temperatures being maintained in the range of from −20 to +40°C.

The aldehydes XIV may be produced from the dithioacetal XI or XIII in a mixture of an organic solvent with water in the presence of a salt of a heavy metal, for example, $HgCl_2$ or an alkyl halide. The organic solvent is especially one which is miscible with water, for example, THF or dioxane, preferably a dipolar aprotic solvent, for example, acetonitrile or DMF. The protecting group is advantageously split off in the presence of an acid-binding agent. The reaction temperatures are generally from 0 to 100°C, preferably from 10 to 60°C.

According to an especially preferred embodiment of this step of the process, the dithioketal XI or XII is stirred in a DMF/water mixture with excess methyl iodide and calcium carbonate for 2 to 5 hours at 30 to 50°C. The aldehyde of formula XIV so obtained may be directly reacted in further steps or may be purified by chromatography after the inorganic salts and the solvent have been eliminated.

Optionally, the unsaturated aldehyde XIV may be hydrogenated to the corresponding saturated aldehyde of formula XV. Suitable processes are those which reduce selectively an isolated olefinic double bond without affecting the aldehyde group. Particularly suitable in this respect is catalytic hydrogenation in the presence of a nickel, palladium or platinum catalyst, optionally on a carrier material, for example, active charcoal or $CaCO_3$. The solvent may be any of those which are generally used for catalytic hydrogenation, for example a low molecular weight alcohol, ester or ether, for example, methanol, ethyl acetate, THF or 1,2 - dimethoxyethane, preferably the compound XIV is hydrogenated in an aprotic solvent, for example, THF, dioxane, 1,2 - dimethoxyethane, an acetic acid ester or acetone in the presence of Raney nickel or palladium on active charcoal, the temperatures being maintained in a range of from 20 to 80°C and the hydrogen pressure in a range of from 1 to 20 atmospheres. In the case where the radical R^5 contains a double or triple bond, this bond is also hydrogenated.

The aldehyde of formula XIV or XV is converted to the compound of formula XVII by reaction with a phosphonium-ylide of formula XVI, wherein the radical R^{10} is preferably a phenyl group, in an appropriate solvent. The phosphonium-ylides and the phosphonium salts on which they are based may be prepared according to methods analogous to those described in the literature (for example Organic Reactions, Vol. 14 (1965), p. 270 sqq., ed. John Wiley and Sons, New York, London, Sidney).

The solution of the resonance stabilized ylide of formula XVI is preferably added in a slight excess to a solution of the aldehyde XIV or XV, and the reaction mixture is preferably heated for 2 to 12 hours to 40—100°C. As the solvent, there may be used an ether, for example, diethyl ether, tetrahydrofuran, diethyleneglycoldimethyl ether, a di-lower alkyl sulfoxide, for example, dimethyl sulfoxide, or an amide of a carboxylic acid, for example, dimethylformamide, N,N-dimethylacetamide or hexamethylphosphoric acid triamide (HMPT), or a hydrocarbon, especially benzene, toluene or xylene.

A preferred embodiment of this stage of the process of the invention is the following: a solution of the methoxycarbonyl - methylene - triphenylphosphorane in toluene is added dropwise and in a slight excess to the solution of the aldehyde XIV or XV in toluene, and the reaction mixture is heated for 4 to 6 hours to 40—80°C in an inert gas atmosphere, for example, under argon, and the completion of the reaction is determined by means of thin layer chromatography. After the usual work-up, the resulting compound of formula XVII is purified by chromatography; However, it may alternatively be employed in the form of the crude product.

The protecting group for the hydroxy group ($R^9{\neq}H$) and the ketal protecting group may be split off simultaneously or one after the other in a reaction *in situ*.

Under gentle conditions, for example, in an alcohol/water mixture containing about 1% by weight of oxalic acid, preferably in ethyleneglycol, in the presence of an acidic catalyst, for example, dichloroacetic acid, boron trifluoride etherate or oxalic acid, at a temperature of from 0 to 30°C, the compounds of formula XVII (R^9=H) are substantially obtained.

Under stronger hydrolysis conditions, the ketal protecting group of the compounds of formula XVII is split off simultaneously with the protecting groups R^9 (in the case where R^9 is not H), and the compounds of formula I according to this invention (R^1 and R^2 together are oxygen, R^3 is H) are obtained. In detail, the operations may be as follows: the compound of formula XVII is dissolved in an ethanol/water mixture containing from 1 to 3% by weight of oxalic acid. The protecting groups are split off at temperatures of from 20 to 50°C and a reaction time of 3 to 24 hours. After evaporation of the solvent at low temperatures, the resulting are advantageously purified by chromatography; however, they may be further reacted directly after the acidic catalyst is removed, for example by distribution of the crude product in water or saturated sodium chloride solution on the one hand and in a nonpolar solution such as benzene on the other.

Under the above conditions, the α,β-unsaturated esters of formula I (R^1 and R^2 together are oxygen, $R^3 \neq H$ and A, R^4 and R^5 are as indicated) are generally difficult to saponify. In order to obtain a compound of formula I wherein R^3 is H, an alkaline hydrolysis with an alkali metal hydroxide in an aqueous-alcoholic solution is advantageously carried out subsequently.

Starting from a compound of formula I, wherein R^1 and R^2 together are oxygen and R^3 is H, the corresponding esters may be prepared very simply, for example, by reaction of the carboxylic acid with a diazoalkane in a solvent, for example, diethyl ether or THF, an aromatic solvent, for example, benzene, or a halogenated hydrocarbon, for example, chloroform.

Another example of a method for preparing an ester of formula I comprises reacting a salt of a carboxylic acid of formula I with an alkyl halide. The solvent for this operation is especially a dipolar, aprotic solvent, for example, acetonitrile, dimethyl formamide or dimethyl sulfoxide; the reaction temperatures are generally in the range of from −10 to +100°C, preferably from 20 to 60°C. In principle, any carboxylic acid of formula I (R^3=H) may be converted to the corresponding ester.

An alcohol of formula I (R^1 and R^2=H or OH; R^1 and R^2 not being identical) may be prepared by reducing the oxo group in the corresponding compound I in which R^1 and R^2 together represent an oxygen atom. As the reducing agent there may be used any substance which reduces an oxo group rather than an ester or acid group and which does not affect the olefinic double bond, if present. Preferred are complex metal hydrides, for example, sodium borohydride, zinc borohydride and lithiumperhydro - 9b - boraphenylalyl hydride. A reducing agent which can reduce a carboxyl group for example, lithiumaluminium hydride may alternatively be employed for this reduction, provided that the reduction is carried out without excess of reducing agent and at low temperatures. On the whole, the reaction conditions described for the preparation of XI from X are valid also in this case.

The reduction of the oxo group at the 1-position of the cyclopentane ring generally does not proceed in a stereo-specific manner. A mixture of α- and β-isomers is obtained. The same goes for the reduction of the oxo group at the 3-position of the lower side chain (reaction X→XI) as well as for the reduction of this oxo group with an organometallic compounds (reaction X→XI and XIV→XV).

The various stereoisomers may be separated directly after their formation or after any of the subsequent reaction steps, which means that all the reactions described may be carried out with the pure α- and β-isomers, respectively, or with an α,β-isomer mixture.

A compound of formula I wherein R^3 is H may be converted to the corresponding metal or ammonium salt by adding the equimolar amount of a base, a carbonate or an amine. Suitable amines are physiologically tolerable primary, secondary or tertiary amines such as triethylamine, benzylamine, tris(hydroxymethyl) - methylamine, piperidine or 4 - ethylmorpholine. Suitable metal ions are those of the alkali metals and alkaline earth metals.

In the compounds II to V, VII, VIII, X, XI, XIII, XIV, XV and XVII, the side chains in 2- and 3-position of the cyclopentane ring may be in the *cis*- or *trans*-position configuration with respect to each other. When the ketal protecting group has been removed, however, the *trans*-configuration of the two side chains occurs preferentially because of thermodynamic reasons. When, therefore, compounds of formula I wherein R^1 and R^2 together are oxygen, or of formula XXII are treated with a base, compounds with side-chains in the *trans*-configuration with respect to each other are preponderantly obtained. Generally, the *trans*-configuration of the side chains is obtained on preparation and purification of these compounds.

The reactions for producing double bonds do not proceed in a completely stereospecific manner, However, it is to be supposed that the Horner reaction, because of the specific mode of operation, produces substantially a *trans*-linkage and the corresponding *cis*-product to an only insignificant extent, which latter is then eliminated by chromatographic purification steps. In a similar manner, the corresponding *trans*-olefin is obtained in the Wittig reaction for the incorporation of carboxyl side chains. Also in this case, the *cis*-olefin occurring to a small extent as by-product may be separated by corresponding purification operations.

When the individual reaction products are not obtained already in sufficiently pure form for use directly for the next reaction step, their purification by means, for example, of column, thin layer or high pressure liquid chromatography is recommended.

The compounds of formula I in accordance with this invention are generally obtained in the form of the racemates, which, optionally, may be obtained in the form of the optically active antipodes according to the usual methods of racemate separation.

Besides the compounds cited in the Examples, the following compounds may also be obtained according to the process of the invention:

7 - [2 - (3 - hydroxy - (*E*) - 1 - octenyl) - 5 - oxo - cyclopentyl] - (*E*) - 2 - heptenoic acid benzyl ester

7 - [2 - (3 - hydroxy - (*E*) - 1 - octenyl) - 5 - oxo - cyclopentyl] - 2 - (*E*) - heptenic acid phenethyl ester

7 - [2 - (3 - hydroxy - (*E*) - 1 - octenyl) - 5 - oxo - cyclopentyl] - 2 - (*E*) - heptenoic acid butyl ester

7 - [2 - (4,4 - dimethyl - 3 - hydroxy - 6 - oxa - (*E*) - 1 - octenyl) - 5 - oxo - cylopentyl] - 2 - (*E*) - heptenoic acid propyl ester

7 - [2 - (3 - hydroxy - 3 - methyl - (*E*) - 1 - octenyl) - 5 - oxo - cyclopentyl] - 2 - (*E*) - heptenoic acid hexyl ester

7 - [2 - (3 - hydroxy - 3 - vinyl - (*E*) - 1 - octenyl) - 5 - oxo - cyclopentyl] - 2 - (*E*) - heptenoic acid ethyl ester

7 - [2 - (4,4 - dimethyl - 3 - hydroxy - 5 - (3 - trifluoromethylphenoxy - (*E*) - 1 - pentenyl) - 5 - oxo - cyclopentyl] - 2 - (*E*) - heptenoic acid heptyl ester

9 - {5 - hydroxy - 2 - (3 - hydroxy - 4 - (3 - chlorophenoxy) - (*E*) - 1 - butenyl] - cyclopenyl} - 2 - (*E*) - heptenoic acid methyl ester

7 - [5 - hydroxy - 3 - (3 - hydroxy - 3 - methyl - (*E*) - 1 - nonenyl) - cyclopentyl] - 2 - (*E*) - heptenoic acid methyl ester

7 - [5 - (3 - hydroxy - 3 - methyl - 6 - oxa - (*E*) - 1 - octenyl) - cyclopentyl] - 2 - (*E*) - heptenoic acid

The compounds of the invention are distinguished on the one hand by spasmogenic properties, and on the other by broncho-dilating, blood pressure lowering, luteolytic, and abortive properties, as well as properties with regard to inhibiting the secretion of gastric juice. They may therefore be used as medicaments.

The invention accordingly provides a pharmaceutical preparation which comprises a compound of the general formula I or a physiologically tolerable salt thereof as active ingredient, in admixture or conjunction with a pharmaceutically suitable carrier.

The pharmaceutical preparations may be in the form of aqueous solutions or suspensions, or may comprise the active ingredient dissolved or suspended in a pharmacologically tolerable organic solvent, for example, a monohydric alcohol or polyol, for example ethanol, ethyleneglycol or glycerol, an oil, for example sunflower oil or cod-liver oil, an ether, for example, diethyleneglycoldimethyl ether, or a polyether, for example, a polyethyleneglycol, or alternatively in the presence of another physiologically tolerable polymer carrier, for example, polyvinylpyrrolidone.

The preparations may be in a form suitable for enteral or parenteral administration, are, for example, infusion and injection solutions and tablets, as well as locally applicable preparations, for example, creams, emulsions, suppositories and, especially, aerosols.

The preparations may comprise one or more further active substances, for example and especially the following:

fertility regulating hormones and releasing hormones, for example, LH, FSH, oestradiol, and LH—RH (LH releasing hormone); diuretics, for example, furosemide; antidiabetics, for example, glycodiazine, tolbutamide, glibenclamide, phenformin, buformin, and metformin; substances effective against circulatory diseases, for example coronary dilators, for example, chromonar or prenylamine, blood pressure lowering products, for example, reserpine, α-methyldopa or clonidine or antiarrhythmics; lipid lowering products, geriatrics and other preparations having effect on the metabolism; psychopharmacological agents for example, chlordiazepoxide, diazepam or meprobamate; vitamins, prostaglandins and prostaglandin-like compounds, furthermore prostaglandin antagonists and prostaglandin biosynthesis inhibitors, for example, non-steroid antiphlogistics.

The suitable daily dose is 1 microgramme to 10 mg/kg body weight; a suitable dosage unit comprises from 0.05 mg to 200 mg of the compound of formula I or a salt thereof.

The compounds of the formulae II, III, V, VII, VIII, X, XI, XIII, XIV, XV and XVII are novel, intermediate compounds for the manufacture of compounds of formula I. Compounds of formula XVII are part of this invention, and certain compounds of formula XVI are described and claimed in our Co-pending Application No. 30062/77. (Serial No. 1589526).

The following Examples illustrate the invention. Ratios of solvents for chromatography are by volume.

EXAMPLE 1

1-(5-acetoxypentyl)-2-oxo-cyclopentanecarboxylic acid ethyl ester

170 g [1.23 mols] of potassium carbonate were added to 180 g [1.15 mols] of 2 - oxocyclopentanecarboxylic acid ethyl ester in 300 ml of dimethylformamide, 281.5 g [1.1 mols] of 5 - acetoxypentyl iodide were added dropwise and the mixture was heated at 100°C for 4 hours. The solvent was distilled off under reduced pressure, the residue digested in diethyl ether, the solvent decanted off the solid residue, the ether washed with water, dried over Na_2SO_4 and distilled off under reduced pressure.

300 g of crude 1 - (5 - acetoxypentyl) - 2 - oxocyclopentane - carboxylic acid ethyl ester were obtained which were used for the following reaction without further purification.

EXAMPLE 2

2-(5-acetoxypentyl)-cyclopentanone

300 g of 1 - (5 - acetoxypentyl) - 2 - oxocyclopentanecarboxylic acid ethyl ester were refluxed for 5 hours in 1.5 l of acetic acid, 600 ml of water and 300 g of sulfuric acid. Subsequently, the solution was concentrated under reduced pressure, 1 liter of semi-saturated sodium chloride solution was added, and the solution was extracted with acetic acid ethyl ester. The organic phase was washed with 500 ml of saturated sodium chloride solution and dried over sodium sulfate. 50 ml of acetic anhydride were added, and the mixture was refluxed for 4 hours. The solvent was distilled off under reduced pressure and the residue was subjected to fractional distillation under reduced pressure in a column having a height of 30 cm.

170 g of a light color oil having a boiling point of 113—117°C at 0.7 mm Hg were obtained.

EXAMPLE 3

2-(5-acetoxypentyl)-cyclopent-2-enone

161 g [0.76 mol] of 2 - (5 - acetoxypentyl) - cyclopentanone were dissolved in 440 ml of carbon tetrachloride, and a solution of 76 ml [0.935 mol] of sulfuryl chloride in 75 ml of carbon tetrachloride was added dropwise with agitation at 10—15°C, and the whole was stirred for 4 hours at room temperature. The solvent was distilled off under reduced pressure, the residue dissolved in toluene, washed with water and bi-carbonate solution and dried over magnesium sulfate. 150 ml [1.25 mols] of 2,4,6 - trimethylpyridine were added to the filtered solution, which was then refluxed with agitation for 15 hours. After cooling, the solution was washed twice with 2 n HCl, once with water and once with sodium bicarbonate solution, dried over sodium sulfate, filtered, and the solvent was distilled off under reduced pressure. The residue was distilled under a reduced pressure of 0.5 mm in a column having a length of 10 cm, and 106 g having a boiling point of 120—125°C at 0.5 mm Hg were obtained.

EXAMPLE 4

2-(5-acetoxypentyl)-3-oxo-cyclopentanecarbonitrile

98 g [1.5 mols] of potassium cyanide were suspended in 600 ml of methanol, and 105 g [0.5 mol] of 2 - (5 - acetoxypentyl) - cyclopent - 2 - enone, dissolved in 45 ml of acetic acid, were added dropwise within 2.5 hours. After a 20 hours agitation at room temperature, the suspension was dropped into ice-water with agitation, extracted thrice with diethyl ether, the ether phases were united, washed with water, dried over sodium sulfate and concentrated. The oily residue was stirred for 5 hours at room temperature in 200 ml of pyridine and 30 ml of acetic anhydride, the solvent was then distilled off under reduced pressure and the residue was distilled in a bulb tube. 102 g having a boiling point of 180°C at 0.4 mm Hg were obtained; IR spectrum: 2220 cm^{-1}.

EXAMPLE 5

2-(5-hydroxypentyl)-3-oxocyclopentanecarbonitrile

102 g of 2 - (5 - acetoxypentyl) - 3 - oxocyclopentanecarbonitrile were stirred for 16 hours at room temperature in 1 l of methanol with 5 ml of concentrated sulfuric acid, 10 g of $NaHCO_3$ were added, the solvent was concentrated under reduced pressure, the oily residue was absorbed in acetic acid ester, washed with water and concentrated.

84.7 g of crude product were obtained which were directly used for the following reaction without any purification. For characterization, an analysis sample was distilled under reduced pressure.

IR: 3400 cm^{-1} (OH)
2240 cm^{-1} (CN)

EXAMPLE 6

2-(4-formylbutyl)-3-oxocyclopentanecarbonitrile

19.5 g [0.1 mol] of 2 - (5 - hydroxypentyl) - 3 - oxocyclopentanecarbonitrile in 30 ml of toluene were added dropwise at –10 to –15°C to a suspension of [0.5 mol]=66.8 g of N - chlorosuccinimide and [0.6 mol]=43.8 ml of dimethyl sulfide in 200 ml of absolute toluene, stirred for 3 hours at –10 to –15°C, subsequently about 75 ml [0.6 mol] of triethylamine were added, agitation was continued for one hour at –10°C, and the reaction mixture was added to the icecold saturated sodium chloride solution. The organic phase was separated, washed to neutral with 1 N HCl, dried and concentrated. 17 g of aldehyde were obtained.

An analysis sample was subjected to chromatography on silica gel.

NMR δ 9.7 large signal, 1H

EXAMPLE 7

2-[4-(1,3-dithiolan-2-yl)-butyl]-3-oxocyclopentanecarbonitrile

17 g[0.063 mol] of 2 - (4 - formylbutyl) - 3 - oxocyclopentanecarbonitrile were dissolved in 200 ml of toluene and stirred for 30 minutes at room temperature with [0.08 mol]=6.7 ml of 1,2 - ethanedithiol and 2 ml of boron trifluoride etherate, washed with water and sodium bicarbonate solution, dried over sodium sulfate and concentrated. 15.6 g of a light color oil were obtained.

An analysis sample was subjected to chromatography on silica gel.

NMR δ	3.2 ppm,	singulet,	4 H
	4.3—4.6 ppm,	triplet,	1 H

EXAMPLE 8

6-[4-(1,3-dithiolan-2-yl)butyl]-1,4-dioxaspiro[4,4]nonane-7-carbonitrile

6.8 g [0.024 mol] of 2 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 3 - oxocyclopentanecarbonitrile were refluxed for 4 hours in a water separator in 200 ml of toluene with 10 ml of 1,2-ethanediol and 3 ml of boron trifluoride etherate, further 10 ml of 1,2 - ethanediol and 3 ml of boron trifluoride etherate were added and the mixture was again refluxed for 3 hours. After cooling, the solution was added to ice water, the organic phase was diluted with diethyl ether and washed with a 5% sodium bicarbonate solution. After drying over magnesium sulfate, the solvent was distilled off under reduced pressure, and 6.4 g of a light color oil were obtained. The analysis sample obtained by chromatography had the following characteristic bands in the NMR spectrum:

δ	4.4—4.7 ppm,	triplet,	1 H
	3.9 ppm,	singlet,	4 H
	3.2 ppm,	singlet,	4 H

EXAMPLE 9

6-[4-(1,3-dithiolan-2-yl)butyl]-1,4-dioxaspiro[4,4]nonane-7-carbaldehyde

13.3 g [0.042 mol] of 6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4]nonane - 7 - carbonitrile were dissolved in 200 ml of toluene, cooled to 5°C, and 9 g [0.064 mol]=about 53 ml of 20% w/v diisobutylaluminium hydride solution in toluene were added dropwise and slowly in such a manner than the temperature did not exceed 7°C. After a reaction time of 2 hours, 15 ml of glacial acetic acid in 30 ml of toluene were added dropwise, subsequently also 50 ml of water, and the mixture was stirred for another 30 minutes. The reaction mixture was then filtered by means of a clarifying layer filter, the organic phase was diluted with ether and separated from the water. After drying over sodium sulfate, the solvent was distilled off under reduced pressure, and 11 g of oily aldehyde were obtained.

The analysis sample was subjected to chromatography on silica gel and showed the following characteristic signals in the NMR spectrum:

δ	9.5—9.7 ppm,	doublet,	1 H
	4.3—4.6 ppm,	triplet,	1 H
	3.9 ppm,	singlet,	4 H
	3.2 ppm,	singlet,	2 H

EXAMPLE 10a

1-{6-[4-(1,3-dithiolan-2-yl)butyl]1,4-dioxaspiro[4,4]-non-7-yl}-1-trans-octen-3-one

[30 millimols]=870 mg of 80% sodium hydride were suspended in 90 ml of 1,2 - dimethoxyethane and [25 millimols]=5.55 g of dimethyl 2 - oxoheptylphosphonate in 100 ml of 1,2 - dimethoxyethane were added dropwise, and the mixture was stirred for 2 hours at room temperature. After this period, a white emulsion had formed, to which a solution of [20 millimols]=6.32 g of 6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4]nonane - 7 - carbaldehyde in 60 ml of 1,2 - dimethoxyethane was added dropwise, and the mixture was stirred for 3 hours at room temperature. Acetic acid was added to this slightly turbid solution until a sample gave a neutral reaction in water. Two spatula tips of animal charcoal were added, and the mixture was filtered by means of a clarifying layer filter. The filtrate was concentrated under reduced pressure, and 6.7 g of a light yellow oil were obtained.

The analysis sample was subjected to chromatography on silica gel and obtained by elution with toluene/acetic acid ester (9:1).

Its NMR data were the following:

δ	5.8 to 7.0 ppm,	multiplet,	2 H
	4.4 ppm,	triplet,	1 H
	3.9 ppm,	singlet,	4 H
	3.2 ppm,	singlet,	4 H

In completely analogous manner, there was prepared from 6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - nonane - 7 - carbaldehyde by reaction with:

EXAMPLE 10b

dimethyl 2-oxononylphosphonate:

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 1 - *trans* - decen - 3 - one.

NMR: δ 5.8—7.0 ppm, multiplet, 2 H

EXAMPLE 10c

dimethyl 2 - cyclohexyl - 2 - oxoethylphosphonate:

1 - {6 - [4 - (1,3 - dithiolan)butyl] - 1,4 - dioxaspiro[4,4]non - 7 - yl} - 3 - cyclohexyl - 1 - *trans* - propen - 3 - one.

NMR: δ 5.8—7.1 ppm, multiplet, 2 H

EXAMPLE 10d

dimethyl - 2 - cycloheptyl - 2 - oxo - ethyl phosphonate:

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 3 - cycloheptyl - 1 - *trans* - propene - 3 - one.

NMR: δ 5.8—7.0 ppm, multiplet, 2 H

EXAMPLE 10e

dimethyl 2 - oxopentylphosphonate:

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 1 - *trans* - hexen - 3 - one.

NMR: δ 5.8—7.0 ppm, multiplet, 2 H

EXAMPLE 10f

In analogous manner,

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 4 - [4 - (4 - chlorophenoxy)phenoxy] - 1 - *trans* - pentene - 3 - one was prepared from dimethyl 3 - [4 - (4 - chlorphenoxy)phenoxy] 2 - oxobutyl phosphonate.

NMR: δ	6.3—7.4 ppm,	multiplet,	10 H
	4.5 ppm,	triplet,	1 H
	3.9 ppm,	singlet,	4 H
	3.15 ppm,	singlet,	4 H

EXAMPLE 10g

In analogous manner,

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 4,4 - dimethyl - 4 - [4 - (4 - chlorophenoxy)phenoxy] - 1 - *trans* - pentene - 3 - one was prepared from dimethyl 3 - methyl - 3 - [4 - (4 - chlorophenoxy)phenoxy]2 - oxobutyl phosphonate.

NMR:	6.8—7.4 ppm,	multiplet,	10 H
	4.5 ppm,	triplet,	1 H
	3.9 ppm,	singlet,	4 H
	3.15 ppm,	singlet,	4 H

EXAMPLE 10h

In analogous manner, there was prepared

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 4 - phenoxy - 1 - trans - buten - 3 - one from dimethyl 3 - phenoxy - 2 - oxopropyl phosphonate.

NMR: δ 6.8—7.5 ppm, multiplet, 5 H

EXAMPLE 10i

In analogous manner,

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 4 - (4 - fluorophenoxy) - 1 - *trans* - buten - 3 - one was prepared from dimethyl 3 - (4 - fluorophenoxy) - 2 - oxopropyl phosphonate.

NMR: δ 6.9—7.3 ppm, multiplet, 4 H

EXAMPLE 10j

In analogous manner,

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 4 - (3 - chlorophenoxy) - 1 - *trans* - buten - 3 - one was prepared from dimethyl 3 - (3 - chlorophenoxy) - 2 - oxopropyl phosphonate.

NMR: δ 6.7—7.5 ppm, multiplet, 4 H

EXAMPLE 10k

In analogous manner,

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 4 - (3 - trifluoromethylphenoxy) - 1 - *trans* - buten - 3 - one was prepared from dimethyl 3 - (3 - trifluoromethyl - phenoxy) - 2 - oxopropyl phosphonate.

NMR: δ 7.0—7.6 ppm, multiplet, 4 H

EXAMPLE 10l

In analogous manner,

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4 - non - 7 - yl} - 5 - methyl - 1 - *trans* - hexen - 3 - one was prepared from dimethyl 4 - methyl - 2 - oxopentyl phosphonate.

NMR: δ	5.9—7 ppm,	multiplet,	2 H
	4.5 ppm,	triplet,	1 H
	3.95 ppm,	singlet,	4 H
	3.2 ppm,	singlet,	4 H

EXAMPLE 10m

In analogous manner,

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4]non - 7 - yl} - 4 - methyl - 1 - *trans* - octen - 3 - one was prepared from dimethyl 3,3 - dimethyl - 2 - oxoheptyl phosphonate.

NMR: δ 5.9—7 ppm, multiplet, 2 H

EXAMPLE 11a

1-{6-[4-(1,3-dithiolan-2-yl)butyl]-1,4-dioxaspiro[4,4]non-7-yl}-1-trans-octen-3-ol

6.2 g [15 millimols] of 1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 1 - *trans* - octen - 3 - one were dissolved in 90 ml of methanol, cooled to 0°C and a solution of [75 millimols]=2.7 g of sodiumborohydride in 30 ml of methanol and 3 ml of water, also cooled to 0°C, was added dropwise. The reaction mixture was then stirred for 3 hours at room temperature, neutralized with acetic acid, and concentrated in a water jet vacuum. The residue was dissolved in diethyl ether and water, and the organic phase was washed several times with water. After evaporation of the solvent under reduced pressure, 6 g of a yellow oil were obtained.

I.R.=3500 cm^{-1}, no carbonyl band

NMR: δ	5.5—5.9 ppm,	multiplet,	2 H
	4.4 ppm,	triplet,	2 H
	3.9 ppm,	singlet,	4 H
	3.2 ppm,	singlet,	4 H

In completely analogous manner, there were prepared

EXAMPLE 11b

from 1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 1 - *trans* - decen - 3 - one:

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 1 - *trans* - decen - 3 - ol.

I.R. 3500 cm^{-1}

NMR: δ 5.5—5.9 ppm, multiplet, 2H

EXAMPLE 11c

from 1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 3 - cyclohexyl - 1 - *trans* - propen - 3 - one:

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 3 - cyclohexyl - 1 - *trans* - propen - 3 - ol.

I.R. 3500 cm^{-1}

NMR: δ 5.5—5.9 ppm, multiplet, 2 H

EXAMPLE 11d

from 1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro - [4,4] - non - 7 - yl} - 3 - cycloheptyl - 1 - *trans* - propen - 3 - one:

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 3 - cycloheptyl - 1 - *trans* - propen - 3 - ol.

I.R. 3500 cm^{-1}

EXAMPLE 11e

from 1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 1 - *trans* - hexen - 3 - one:

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 1 - *trans* - hexen - 3 - ol.

I.R. 3500 cm^{-1}

EXAMPLE 11f

In analogy to Example 11a, there was prepared from

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 4 - [4 - (4 - chlorophenoxy) - phenoxy] - 1 - *trans* - penten - 3 - one:

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 4 - [4 - (4 - chlorophenoxy)phenoxy] - 1 - *trans* - penten - 3 - ol.

I.R. 3500 cm^{-1}

EXAMPLE 11g

In analogy to Example 11a, there was prepared from

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl[- 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 4 - methyl - 4 - [4 - (4 - chlorophenoxy)phenoxy] - 1 - *trans* - penten - 3 - one:

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 4 - methyl - 4 - [4 - (4 - chlorophenoxy)phenoxy] - 1 - *trans* - penten - 3 - ol.

I.R. 3500 cm^{-1}

EXAMPLE 11h

In analogy to Example 11a, there was prepared from

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 4 - phenoxy - 1 - *trans* - buten - 3 - one:

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 4 - phenoxy - 1 - *trans* - buten - 3 - ol.

I.R. 3500 cm^{-1}

EXAMPLE 11i

In analogy to Example 11a, there was prepared from

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 4 - (4 - fluorophenoxy) - 1 - *trans* - buten - 3 - one:

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 4 - (4 - fluorophenoxy) - 1 - *trans* - buten - 3 - ol.

I.R. 3500 cm^{-1}

EXAMPLE 11j

In analogy to Example 11a, there was prepared from

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 4 - (3 - chlorophenoxy) - 1 - *trans* - buten - 3 - one:

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 4 - (3 - chlorophenoxy) - 1 - *trans* - buten - 3 - ol.

I.R. 3500 cm^{-1}

EXAMPLE 11k

In analogy to Example 11a, there was prepared from

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 4 - (3 - trifluoromethylphenoxy) - 1 - *trans* - buten - 3 - one:

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 4 - (3 - trifluoromethylphenoxy) - 1 - *trans* - buten - 3 - ol.

I.R. 3500 cm^{-1}

EXAMPLE 11l

In analogy to Example 11a, there was prepared from

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 5 - methyl - 1 - *trans* - hexen - 3 - one:

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 5 - methyl - 1 - *trans* - hexen - 3 - ol.

I.R. 3500 cm^{-1}

EXAMPLE 11m

In analogy to Example 11a, there was prepared from

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 4,4 - dimethyl - 1 - *trans* - octen - 3 - one:

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 4,4 - dimethyl - 1 - *trans* - octen - 3 - ol.

I.R. 3500 cm^{-1}

NMR: δ 5.3—5.7 ppm, multiplet, 2 H

EXAMPLE 12a

1-{6-[4-(1,3-dithiolan-2-yl)butyl]-1,4-dioxaspiro[4,4]-non-7-yl}-1-trans-octen-3-ol tetrahydropyran-2-yl ether

3.82 g [9.2 millimols] of 1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4]non - 7 - yl} - 1 - *trans* - octen - 3 - ol were stirred for 4 hours at room temperature in 75 ml of diethyl ether with 4.2 ml of 2,3 - dihydropyran and 80 mg of *p* - toluenesulfonic acid. Subsequently, the batch was stirred for 15 minutes with 1 g of solid sodium carbonate. After filtration, the filtrate was concentrated under reduced pressure, and 3.9 g of a light yellow oil were obtained. An analytically pure sample was obtained by chromatography on silica gel and elution with toluene/acetic acid ester (9:1).

NMR: δ	5.4—5.7 ppm,	multiplet,	4 H
	4.4—4.8 ppm,	multiplet,	2 H
	3.9 ppm,	singlet,	4 H
	3.2 ppm,	singlet,	4 H

In a completely analogous manner, the following tetrahydropyranyl ethers were prepared from the alcohols according to Examples 11b to 11m respectively:

EXAMPLE 12b

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 1 - *trans* - decen - 3 - ol tetrahydropyran - 2 - yl ether.

NMR: δ 4.5—4.8 ppm, multiplet, 2 H

EXAMPLE 12c

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 3 - cyclohexyl - 1 - *trans* - propen - 3 - ol tetrahydropyran - 2 - yl ether.

NMR: δ 4.5—4.8 ppm, multiplet, 2 H

EXAMPLE 12d

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 3 - cycloheptyl - 1 - *trans* - propen - 3 - ol tetrahydropyran - 2 - yl ether.

NMR: δ 4.5—4.8 ppm, multiplet, 2 H

EXAMPLE 12e

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 1 - *trans* - hexen - 3 - ol tetrahydropyran - 2 - yl ether.

NMR: δ 4.5—4.8 ppm, multiplet, 2 H

EXAMPLE 12f

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 4 - [4 - (4 - chlorophenoxy)phenoxy] - 1 - *trans* - penten - 3 - ol tetrahydropyran - 2 - yl ether.

NMR: δ 4.5—4.8 ppm, multiplet, 2 H

EXAMPLE 12g

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 4 - methyl - 4 - [4 - (4 - chlorophenoxy)phenoxy] - 1 - *trans* - penten - 3 - ol tetrahydropyran - 2 - yl ether.

NMR: δ 4.5—4.8 ppm, multiplet, 2 H

EXAMPLE 12h

1 - {6 - [4 - (1,3 - dithia - 2 - cyclopentyl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 4 - phenoxy - 1 - trans - butene - 3 - ol - tetrahydropyranyl ether.

NMR: δ 4.5—4.8 ppm, multiplet, 2H

EXAMPLE 12i

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4]non - 7 - yl} - 4 - (4 - fluorophenoxy) - 1 - *trans* - buten - 3 - ol tetrahydropyran - 2 - yl ether.

NMR: δ 4.5—4.8 ppm, multiplet, 2 H

EXAMPLE 12j

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 4 - (3 - chlorophenoxy) - 1 - *trans* - buten - 3 - ol - tetrahydropyran - 2 - yl ether.

NMR: δ 4.5—4.8 ppm, multiplet, 2 H

EXAMPLE 12k

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 4 - (3 - trifluoromethylphenoxy) - 1 - *trans* - buten - 3 - ol tetrahydropyran - 2 - yl ether.

NMR: δ 4.5—4.8 ppm, multiplet, 2 H

EXAMPLE 12l

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 5 - methyl - 1 - *trans* - hexen - 3 - ol tetrahydropyran - 2 - yl ether.

NMR: δ 4.5—4.8 ppm, multiplet, 2 H

EXAMPLE 12m

1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4,4] - non - 7 - yl} - 4,4 - dimethyl - 1 - *trans* - octen - 3 - ol tetrahydropyran - 2 - yl ether.

NMR: δ 4.5—4.8 ppm, multiplet, 2 H

EXAMPLE 13a

5-[7-(3-tetrahydropyran-2′-yloxy-1-*trans*-octenyl)-1,4-dioxaspiro[4,4]-non-6-yl]pentanal

3.9 g [7.8 millimols] of 1 - {6 - [4 - (1,3 - dithiolan - 2 - yl) - butyl] - 1,4 - dioxaspiro[4,4]non - 7 - yl} - 1 - *trans* - octen - 3 - ol tetrahydropyran - 2 - yl ether were dissolved in 40 ml of dimethylformamide, 62.4 millimols=6.24 g of $CaCO_3$ and 1.1 ml of H_2O were added and, after addition of 6.93 g [54.6 millimols] of methyl iodide the batch was stirred for 3 hours at 60°C. After cooling, acetone was added to the solution, which was then filtered. The filtrate was evaporated to dryness under reduced pressure, the residue was dissolved in ether, washed with water, dried over magnesium sulfate, filtered, and the solvent was distilled off under reduced pressure. 3.2 g of a brown oil were obtained.

The analysis sample, dissolved in diethyl ether, was filtered via a silica gel column.

NMR: δ	5.3—5.7 ppm,	multiplet,	2 H
	8.7 ppm,	(c), large signal	1 H
I.R.	1730 cm^{-1}		

In a completely analogous manner, the following aldehydes were obtained from the tetrahydropyranyl ethers according to Examples 12b to 12m respectively:

EXAMPLE 13b

5 - [7 - (3 - tetrahydropyran - 2′ - yloxy - 1 - *trans* - decenyl) - 1,4 - dioxaspiro - [4,4]non - 6 - yl]pentanal

I.R. 1730 cm^{-1}

EXAMPLE 13c

5 - [7 - (3 - cyclohexyl - 3 - tetrahydropyran - 2′ - yloxy - 1 - *trans* - propenyl) - 1,4 - dioxaspiro[4,4]non - 6 - yl]pentanal.

I.R. 1730 cm^{-1}

EXAMPLE 13d

5 - [7 - (3 - cycloheptyl - 3 - tetrahydropyran - 2′ - yloxy - 1 - *trans* - propenyl) - 1,4 - dioxaspiro[4,4]non - 6 - yl] pentanal.

I.R. 1730 cm^{-1}

EXAMPLE 13e

5 - [7 - (3 - tetrahydropyran - 2′ - yloxy - 1 - *trans* - hexenyl)1,4 - dioxaspiro - [4,4]non - 6 - yl]pentanal.

I.R. 1730 cm^{-1}

EXAMPLE 13f

5 - {[7 - {3 - tetrahydropyran - 2′ - yloxy - 4 - [4 - (4 - chlorophenoxy) - phenoxy] - 1 - *trans* - pentenyl} - 1,4 - dioxaspiro[4,4]non - 6 - yl]} - pentanal.

I.R. 1730 cm^{-1}

EXAMPLE 13g

5 - {[7 - {3 - tetrahydropyran - 2′ - yloxy - 4 - methyl - 4 - [4 - chlorophenoxy) - phenoxy] - 1 - *trans* - pentenyl} - 1,4 - dioxaspiro[4,4]non - 6 - yl]} - pentanal.

I.R. 1730 cm^{-1}

EXAMPLE 13h

5 - [7 - (3 - tetrahydropyran - 2′ - yloxy - 4 - phenoxy - 1 - *trans* - butenyl) - 1,4 - dioxaspiro[4,4]non - 6 - yl] - pentanal.

I.R. 1730 cm^{-1}

EXAMPLE 13i

5 - {7 - [3 - tetrahydropyran - 2′ - yloxy - 4 - (4 - fluorophenoxy) - 1 - *trans* - butenyl] - 1,4 - dioxaspiro[4,4]non - 6 - yl}pentanal.

I.R. 1730 cm^{-1}

EXAMPLE 13j

5 - {7 - [3 - tetrahydropyran - 2′ - yloxy - 4 - (3 - chlorophenoxy) - 1 - *trans* - butenyl] - 1,4 - dioxaspiro[4,4]non - 6 - yl} - pentanal.

I.R. 1730 cm^{-1}

EXAMPLE 13k

5 - {7 - [3 - tetrahydropyran - 2′ - yloxy - 4 - (3 - trifluoromethyl) - 1 - *trans* - butenyl] - 1,4 - dioxaspiro[4,4]non - 6 - yl} - pentanal.

I.R. 1730 cm^{-1}

EXAMPLE 13l

5 - [7 - (3 - tetrahydropyran - 2′ - yloxy - 5 - methyl - 1 - *trans* - hexenyl) - 1,4 - dioxaspiro[4,4]non - 6 - yl]pentanal.

I.R. 1730 cm^{-1}

EXAMPLE 13m

5 - [7 - (3 - tetrahydropyran - 2′ - yloxy - 4,4 - dimethyl - 1 - *trans* - octenyl) - 1,4 - dioxaspiro[4,4]non - 7 - yl] - pentanal.

I.R. 1730 cm^{-1}

EXAMPLE 14a

7-[7-(3-tetrahydropyran-2′-yloxy-1-*trans*-octenyl)-1,4-dioxaspiro-[4,4]non-6-yl]-2-*trans*-heptenoic acid methyl ester

2.78 g [6.6 millimols] of 5 - [7 - (3 - tetrahydropyran - 2′ - yloxy) - 1 - *trans* - octenyl) - 1,4 - dioxaspiro[4,4]non - 6 - yl] pentanal were refluxed with 2.88 g [8.6 millimols] of methoxycarbonyl - methylenetriphenylphosphorane in 200 ml of toluene for 8 hours. The solvent was distilled off under reduced pressure, and the residue, dissolved in diethyl ether, filtered *via* a silica gel column. The ether was evaporated, and 2.6 g of a light color oil were obtained.

NMR: δ	5.2—7.2 ppm,	large multiplet,	4 H
	3.9 ppm,	singulet,	4 H
	3.7 ppm,	singulet,	3 H

In analogous manner, the following esters were synthetized from the pentane aldehydes obtained according to Examples 13b to 13m respectively:

EXAMPLE 14b

7 - [7 - (3 - tetrahydropyran - 2′ - yloxy - 1 - *trans* - decenyl) - 1,4 - dioxaspiro - [4,4] - non - 6 - yl] - 2 - *trans* - heptenoic acid methyl ester.

NMR: δ	3.9 ppm,	singlet,	4 H
	3.7 ppm,	singlet,	3 H

EXAMPLE 14c

7 - [7 - (3 - cyclohexyl - 3 - tetrahydropyran - 2′ - yloxy - 1 - *trans* - propenyl) - 1,4 - dioxaspiro[4,4]non - 6 - yl] - 2 - *trans* - heptenoic acid methyl ester.

NMR: δ 3.9 ppm, singlet, 4 H
3.7 ppm, singlet, 3 H

EXAMPLE 14d

7 - [7 - (3 - cycloheptyl - 3 - tetrahydropyran - 2′ - yloxy - 1 - *trans* - propenyl) - 1,4 - dioxaspiro[4,4]non - 6 - yl] - 2 - *trans* - heptenoic acid methyl ester.

NMR: δ 3.9 ppm, singlet, 4 H
3.7 ppm, singlet, 3 H

EXAMPLE 14e

7 - [7 - (3 - tetrahydropyran - 2′ - yloxy - 1 - *trans* - hexenyl) - 1,4 - dioxaspiro - [4,4]non - 6 - yl] - 2 - *trans* - heptenoic acid methyl ester.

NMR: δ 3.9 ppm, singlet, 4 H
3.7 ppm, singlet, 3 H

EXAMPLE 14f

7 - {{7 - {3 - tetrahydropyran - 2′ - yloxy - 4 - [4 - chlorophenoxy) - phenoxy] - 1 - *trans* - pentenyl} - 1,4 - dioxaspiro[4,4]non - 6 - yl}}2 - *trans* - heptenoic acid methyl ester.

NMR: δ 3.9 ppm, singlet, 4 H
3.7 ppm, singlet, 3 H

EXAMPLE 14g

7 - {{7 - {3 - tetrahydropyran - 2′ - yloxy - 4 - methyl - 4 - [4 - (chlorophenoxy) - phenoxy] - 1 - *trans* - 1 - pentenyl} - 1,4 - dioxaspiro[4,4]non - 6 - yl}} - 2 - *trans* - heptenoic acid methyl ester.

NMR: δ 3.9 ppm, singlet, 4 H
3.7 ppm, singlet, 3 H

EXAMPLE 14h

7 - [7 - (3 - tetrahydropyran - 2′ - yloxy - 4 - phenoxy - 1 - *trans* - butenyl) - 1,4 - dioxaspiro[4,4]non - 6 - yl] - 2 - *trans* - heptenoic acid methyl ester.

NMR: δ 3.9 ppm, singlet, 4 H
3.7 ppm, singlet, 3 H

EXAMPLE 14i

7 - {7 - [3 - tetrahydropyran - 2′ - yloxy - 4 - (4 - fluorophenoxy) - 1 - *trans* - butenyl]1,4 - dioxaspiro[4,4]non - 6 - yl} - 2 - *trans* - heptenoic acid methyl ester.

NMR: δ 3.9 ppm, singlet, 4 H
3.7 ppm, singlet, 3 H

EXAMPLE 14j

7 - {7 - [3 - tetrahydropyran - 2′ - yloxy - 4 - (3 - chlorophenoxy) - 1 - *trans* - butenyl]1,4 - dioxaspiro[4,4]non - 6 - yl} - 2 - *trans* - heptenoic acid methyl ester.

NMR: δ 3.9 ppm, singlet, 4 H
3.7 ppm, singlet, 3 H

EXAMPLE 14k

7 - {7 - [3 - tetrahydropyran - 2′ - yloxy - 4 - (3 - trifluoromethylphenoxy) - 1 - *trans* - butenyl] - 1,4 - dioxaspiro[4,4]non - 6 - yl} - 2 - *trans* - heptenoic acid methyl ester.

NMR: δ 3.9 ppm, singlet, 4 H
3.7 ppm, singlet, 3 H

EXAMPLE 14l

7 - [7 - (3 - tetrahydropyran - 2′ - yloxy - 5 - methyl - 1 - *trans* - hexenyl) - 1,4 - dioxaspiro[4,4]non - 6 - yl] - 2 - *trans* - heptenoic acid methyl ester.

NMR: δ 3.9 ppm, singlet, 4 H
3.7 ppm, singlet, 3 H

EXAMPLE 14m

7 - [7 - (3 - tetrahydropyran - 2′ - yloxy - 4,4 - dimethyl - 1 - *trans* - octenyl) - 1,4 - dioxaspiro[4,4]non - 7 - yl] - 2 - *trans* - heptenoic acid methyl ester.

NMR: δ 3.9 ppm, singlet, 4 H
3.7 ppm, singlet, 3 H

EXAMPLE 15a

7-[2-(3-hydroxy-1-*trans*-octenyl)-5-oxocyclopentyl]-2-*trans*-heptenoic acid methyl ester

2 g [4.2 millimols] of 7 - [7 - (3 - tetrahydropyran - 2′ - yloxy - 1 - *trans* - octenyl) - 1,4 - dioxaspiro[4,4]non - 6 - yl] - 2 - *trans* - heptenoic acid methyl ester were stirred for 8 hours at 40°C in 200 ml of ethanol with 20 ml of 10% w/v aqueous oxalic acid, and subsequently, the solvent was concentrated under reduced pressure. The residue was dissolved in diethyl ether and water, the organic phase was washed several times with water and, after drying over magnesium sulfate, the solvent was removed under reduced pressure. 1.3 g of a light color oil were obtained.

NMR: δ 3.7 ppm, singlet, 3 H

600 mg of this oil were subjected to chromatography on silica gel and, by elution with cyclohexane/acetic acid ester (9:1), 240 mg of rapidly migrating isomer=isomer B, and 160 mg of a slowly migrating isomer=isomer A were obtained. In complete analogy, the following heptenic acid esters were obtained from the corresponding substituted heptenic acid esters prepared according to the Examples 14b to 14m respectively:

EXAMPLE 15b

7 - [2 - (3 - hydroxy - 1 - *trans* - decenyl) - 5 - oxocyclopentyl] - 2 - *trans* - heptenoic acid methyl ester.

NMR: δ 3.7 ppm, singlet, 3 H

EXAMPLE 15c

7 - [2 - (3 - cyclohexyl - 3 - hydroxy - 1 - *trans* - propenyl) - 5 - oxocyclopentyl] - 2 - *trans* - heptenoic acid methyl ester.

NMR: δ 3.7 ppm, singlet, 3 H

EXAMPLE 15d

7 - [2 - (3 - cycloheptyl - 3 - hydroxy - 1 - *trans* - propenyl) - 5 - oxocyclopentyl] - 2 - *trans* - heptenoic acid methyl ester.

NMR: δ 3.7 ppm, singlet, 3 H

EXAMPLE 15e

7 - [2 - (3 - hydroxy - 1 - *trans* - hexenyl) - 5 - oxocyclopentyl] - 2 - *trans* - heptenoic acid methyl ester.

NMR: δ 3.7 ppm, singlet, 3 H

EXAMPLE 15f

7 - {[2 - {3 - hydroxy - 4 - [4 - (4 - chlorophenoxy)phenoxy] - 1 - *trans* - pentenyl} - 5 - oxocyclopentyl]} - 2 - *trans* - heptenoic acid methyl ester.

NMR: δ 3.7 ppm, singlet, 3 H

EXAMPLE 15g

7 - {[- 2 - {3 - hydroxy - 4 - methyl - 4 - [4 - (4 - chlorophenoxy)phenoxy] - 1 - *trans* - pentenyl} - 5 - oxocyclopentyl]} - 2 - *trans* - heptenoic acid methyl ester.

NMR: δ 3.7 ppm, singlet, 3 H

EXAMPLE 15h

7 - [2 - (3 - hydroxy - 4 - phenoxy - 1 - *trans* - butenyl) - 5 - oxocyclopentyl] - 2 - *trans* - heptenoic acid methyl ester.

NMR: δ 3.7 ppm, singlet, 3 H

EXAMPLE 15i

7 - {2 - [3 - hydroxy - 4 - (4 - fluorophenoxy) - 1 - *trans* - butenyl] - 5 - oxo - cyclopentyl} - 2 - trans - heptenoic acid methyl ester.

NMR: δ 3.7 ppm, singlet, 3 H

EXAMPLE 15j

7 - {2 - [3 - hydroxy - 4 - (3 - chlorophenoxy) - 1 - *trans* - butenyl] - 5 - oxocyclopentyl} - 2 - *trans* - heptenoic acid methyl ester.

NMR: δ 3.7 ppm, singlet, 3 H

EXAMPLE 15k

7 - {2 - [3 - hydroxy - 4 - (3 - trifluoromethylphenoxy) - 1 - *trans* - butenyl] - 5 - oxocyclopentyl} - 2 - *trans* - heptenoic acid methyl ester.

NMR: δ 3.7 ppm, singlet, 3 H

EXAMPLE 15l

7 - [2 - (3 - hydroxy - 5 - methyl - 1 - *trans* - hexenyl) - 5 - oxocyclopentyl] - 2 - *trans* - heptenoic acid methyl ester.

NMR: δ 3.7 ppm, singlet, 3 H

EXAMPLE 15m

7 - [2 - (3 - hydroxy - 4 - methyl - 1 - *trans* - octenyl) - 5 - oxocyclopentyl] - 2 - *trans* - heptenoic acid methyl ester.

NMR: δ 3.7 ppm, singlet, 3 H

EXAMPLE 16a

7-[2-(3-hydroxy-1-*trans*-octenyl)-5-oxocyclopentyl]-2-*trans*-heptenoic acid

340 mg of 7 - [2 - (3 - hydroxy - 1 - *trans* - octenyl) - 5 - oxocyclopentyl] - 2 - *trans* - heptenoic acid methyl ester isomer B were stirred at room temperature for 60 hours with 1 N NaOH in aqueous methanol and 280 mg of crude acid were isolated by acidification and extraction with ether.

The analytically pure substance gave the following analysis results:

NMR: δ	5.5—7.2	several multiplets,	6 H
	4.2 (c)	multiplet,	1 H

In a completely analogous manner, the following heptenic acids were obtained from the corresponding substituted heptenic acid esters prepared according to the Examples 15b to 15m respectively:

EXAMPLE 16b

7 - [2 - (3 - hydroxy - 1 - *trans* - decenyl) - 5 - oxocyclopentyl] - 2 - *trans* - heptenoic acid.

NMR: δ	6.7—7.8,	multiplet,	3 H
	5.5—6.0,	multiplet,	3 H
	3.8—4.2,	multiplet,	1 H

EXAMPLE 16c

7 - [2 - (3 - cyclohexyl - 3 - hydroxy - 1 - *trans* - propenyl) - 5 - oxocyclopentyl] - 2 - *trans* - heptenoic acid.

NMR: δ	6.7—7.8,	multiplet,	3 H
	5.5—6.0,	multiplet,	3 H
	3.8—4.1,	multiplet,	1 H

EXAMPLE 16d

7 - [2 - (3 - cycloheptyl - 3 - hydroxy - 1 - *trans* - propenyl) - 5 - oxocyclopentyl] - 2 - *trans* - heptenoic acid.

NMR: δ	6.7—7.9	multiplet,	3 H
	5.5—6.0	multiplet,	3 H
	3.8—4.1	multiplet,	1 H

EXAMPLE 16e

7 - [2 - (3 - hydroxy - 1 - *trans* - hexenyl) - 5 - oxocyclopentyl] - 2 - *trans* - heptenoic acid.

NMR: δ	6.7—8.0	multiplet,	3 H
	5.5—6.0	multiplet,	3 H
	3.8—4.1,	multiplet,	1 H

EXAMPLE 16f

7 - {{2 - {3 - hydroxy - 4 - [4 - (4 - chlorophenoxy)phenoxy] - 1 - *trans* - pentenyl} - 5 - oxocyclopentyl}} - 2 - *trans* - heptenoic acid.

NMR: δ	6.7—7.9	multiplet,	11 H
	5.5—6.0	multiplet,	3 H
	3.8—4.1	multiplet,	1 H

EXAMPLE 16g

7 - {{2 - { - 3 - hydroxy - 4 - methyl - 4 - [4 - (4 - chlorphenoxy)phenoxy] - 1 - *trans* - pentenyl} - 5 - oxocyclophentyl}} - 2 - *trans* - heptenoic acid.

NMR: δ	6.7—8.0	multiplet,	11 H
	5.4—6.0	multiplet,	3 H
	3.9—4.2	multiplet,	1 H

EXAMPLE 16h

7 - [2 - (3 - hydroxy - 4 - phenoxy - 1 - *trans* - butenyl) - 5 - oxocyclopentyl] - 2 - *trans* - heptenoic acid.

NMR: δ	6.7—8.1	multiplet,	8 H
	5.4—6.0	multiplet,	3 H
	3.8—4.2	multiplet,	3 H

EXAMPLE 16i

7 - {2 - [3 - hydroxy - 4 - (4 - fluorophenoxy) - 1 - *trans* - butenyl] - 5 - oxocyclopentyl} - 2 - *trans* - heptenoic acid.

NMR: δ	6.6—8.0	multiplet,	7 H
	5.4—6.0	multiplet,	3 H
	3.7—4.2	multiplet,	3 H

EXAMPLE 16j

7 - {2 - [3 - hydroxy - 4 - (3 - chlorophenoxy) - 1 - *trans* - butenyl] - 5 - oxocyclopentyl} - 2 - *trans* - heptenoic acid.

NMR: δ	6.4—8.1	multiplet,	7 H
	5.4—6.1	multiplet,	3 H
	3.7—4.2	multiplet,	3 H

EXAMPLE 16k

7 - {2 - [3 - hydroxy - 4 - (3 - trifluoromethylphenoxy) - 1 - *trans* - butenyl] - 5 - oxocyclopentyl} - 2 - *trans* - heptenoic acid.

NMR: δ	5.5—7.5	several multiplets + singlet	10 H
	4.5	multiplet	1 H

EXAMPLE 16l

7 - [2 - (3 - hydroxy - 5 - methyl - 1 - *trans* - hexenyl) - 5 - oxocyclopentyl] - 2 - *trans* - heptenoic acid.

NMR: δ	6.7—7.8	multiplet,	3 H
	5.5—6.0	multiplet,	3 H
	3.7—4.2	multiplet,	1 H

EXAMPLE 16m

7 - [2 - (3 - hydroxy - 4,4 - dimethyl - 1 - *trans* - octenyl) - 5 - oxocyclopentyl] - 2 - *trans* - heptenoic acid.

NMR: δ	6.7—7.8	multiplet,	3 H
	5.5—6.0	multiplet,	3 H
	3.6—3.8	multiplet,	1 H
	0.8—0.9	2 singulet,	6 H

EXAMPLE 17a

7-[2-(3-hydroxy-1-*trans*-octenyl)-5-hydroxycyclopentyl]-2-trans-heptenoic acid

140 mg of 7 - [2 - (3 - hydroxy - 1 - *trans* - octenyl) - 5 - oxocyclopentyl] - 2 - *trans* - heptenoic acid were dissolved in 10 ml methanol, 400 mg of $NaBH_4$ were added and the mixture was stirred overnight at room temperature, subsequently glacial acetic acid was saturated sodium chloride solution were added, and the batch was then extracted 3 times by shaking with 50 ml of diethyl ether. The combined ether extracts were washed with water, dried and concentrated, and 118 mg of light color oil were obtained.

NMR: δ 5—7 ppm, several multiplets, 7 H
I.R. large band at 3500 cm^{-1}

The following 5-hydroxy compounds were obtained analogously from the corresponding 5-oxo-compounds of examples 16b to 16m respectively:

EXAMPLE 17b

7 - [2 - (3 - hydroxy - 3 - heptyl - 1 - *trans* - propenyl) - 5 - hydroxycyclopentyl] - 2 - *trans* - heptenoic acid.

I.R. 3500 cm^{-1}

EXAMPLE 17c

7 - [2 - (3 - hydroxy - 3 - cyclohexyl - 1 - *trans* - propenyl) - 5 - hydroxycyclopentyl] - 2 - *trans* - heptenoic acid.

I.R. 3500 cm^{-1}

EXAMPLE 17d

7 - [2 - (3 - hydroxy - 3 - cycloheptyl - 1 - *trans* - propenyl) - 5 - hydroxycyclopentyl] - 2 - *trans* - heptenoic acid.

I.R. 3500 cm^{-1}

EXAMPLE 17e

7 - [2 - (3 - hydroxy - 1 - *trans* - hexenyl) - 5 - hydroxycyclopentyl] - 2 - *trans* - heptenoic acid.

I.R. 3500 cm^{-1}

EXAMPLE 17f

7 - {{2 - {3 - hydroxy - 4 - [4 - (4 - chlorophenoxy)phenoxy] - 1 - *trans* - pentenyl} - 5 - hydroxycyclopentyl}} - 2 - *trans* - heptenoic acid.

I.R. 3500 cm^{-1}

EXAMPLE 17g

7 - {{2 - {3 - hydroxy - 4 - methyl - 4 - [4 - (4 - chlorophenoxy)phenoxy] - 1 - *trans* - pentenyl} - 5 - hydroxycyclopentyl}} - 2 - *trans* - heptenoic acid.

I.R. 3500 cm^{-1}

EXAMPLE 17h

7 - [2 - (3 - hydroxy - 4 - phenoxy - 1 - *trans* - butenyl) - 5 - hydroxycyclopentyl] - 2 - *trans* - heptenoic acid.

I.R. 3500 cm^{-1}

EXAMPLE 17i

7 - {2 - [3 - hydroxy - 4 - (4 - fluorophenoxy) - 1 - *trans* - butenyl] - 5 - hydroxycyclopentyl} - 2 - *trans* - heptenoic acid.

I.R. 3500 cm^{-1}

EXAMPLE 17j

7 - {2 - [3 - hydroxy - 4 - (3 - chlorophenoxy) - 1 - *trans* - butenyl] - 5 - hydroxycyclopentyl} - 2 - *trans* - heptenoic acid.

I.R. 3500 cm^{-1}

EXAMPLE 17k

7 - {2 - [3 - hydroxy - 4 - (3 - trifluoromethylphenoxy) - 1 - *trans* - butenyl] - 5 - hydroxycyclopentyl} - 2 - *trans* - heptenoic acid.

I.R. 3500 cm^{-1}

EXAMPLE 17l

7 - [2 - (3 - hydroxy - 5 - methyl - 1 - *trans* - hexenyl) - 5 - hydroxy - cyclopentyl] - 2 - *trans* - heptenoic acid.

I.R. 3500 cm^{-1}

EXAMPLE 17m

7 - [2 - (3 - hydroxy - 4,4 - dimethyl - 1 - *trans* - octenyl - 5 - hydroxycyclopentyl] - 2 - *trans* - heptenoic acid.

I.R. 3500 cm^{-1}

EXAMPLE 18

7-[2-(3-Hydroxy-3-methyl-1-trans-octenyl)-5-oxo-cyclopentyl]-2-trans-heptenic acid

a) 1 - {6 - [4 - (1,3 - dithiolan - 2 - yl)butyl] - 1,4 - dioxaspiro[4.4] - non - 7 - yl} - 3 - hydroxy - 3 - methyl - 1 - trans - octene

2.0 g of the product of Example 10a were dissolved in 100 ml of absolute ether, and 10 ml of a 2 molar ether/methyl lithium solution were added dropwise under an argon atmosphere at room temperature. After 1/2 hour, the batch was cooled to 10°C, and 20 ml of ice water were added dropwise. Subsequently, the ether phase was separated, the aqueous phase was saturated with sodium chloride and extracted several times with ether. The united ether phases were washed with sodium chloride solution, dried and evaporated. For purification, chromatography was carried out on silica gel with cyclohexane/acetic acid ester (9/1). 1.03 g of the intended alcohol were obtained.

TLC (Merck instant sheets, cyclohexane/acetic acid ester 1/1) Rf~0.55

b) 5 - [7 - (3 - hydroxy - 3 - methyl - 1 - trans - octenyl) - 1,4 - dioxaspiro[4,4] - non - 6 - yl] - pentanal

was obtained from the product of a) by selective removal of the thioacetal group, that is, 1.03 g of the above product were dissolved in 15 ml of absolute DMSO, 2.15 g of calcium carbonate, 0.5 ml of water and 1.1 ml of methyl iodide were added, and the mixture was heated to 65°C. After 2 hours 1/2, the reaction was complete. The calcium carbonate was suction-filtered, and the filter residue was washed with ether. The filtrate was shaken with ice water and ether. The ether phase was separated, washed with sodium thiosulfate solution, dried and evaporated. 656 mg of the desired aldehyde were obtained.

TLC (diluent as sub a): Rf 0.35, stainable with 2.4-dinitrophenylhydrazine+dimethylaminobenzaldehyde.

c) 7 - [7 - (3 - hydroxy - 3 - methyl - 1 - trans - octenyl) - 1,4 - dioxaspiro [4,4] - non - 6 - yl] - 2 - *trans* - heptenoic acid methyl ester

656 mg of the aldehyde prepared according to b) were dissolved in 25 ml of benzene and refluxed for 2 hours 1/2 together with 1.25 g of carbomethoxymethylene-triphenylphosphorane. Subsequently, the reaction solution was evaporated, the residue was thoroughly triturated with ether and the insoluble substances were filtered off. The filtrate was evaporated and subjected to chromatography with cyclohexane/acetic acid ester 8/2 as diluent. 453 mg of the desired final product were obtained.

d) 7 - [2 - (3 - hydroxy - 3 - methyl - 1 - *trans* - octenyl) - 5 - oxocyclopentyl] - 2 - *trans* - heptenoic acid methyl ester

In order to split off the ethyleneketal group, the product obtained according to c) was dissolved in 7.5 ml of 1,2-dimethoxy-ethane and stirred at room temperature for 2 hours together with 7.5 ml of methanol, 4.5 ml of 10% w/v aqueous oxalic acid and 4.5 ml of water. The batch was then poured onto ice water and several times extracted with chloroform. The residue was subjected to chromatography on silica gel with cyclohexane/acetic acid ester 9/1. 287 mg of the desired ester were obtained.

TLC (diluent as sub a): Rf~0.42

NMR (60 MHz, $CDCl_3$):

(ppm)	6.7—7.3	1H dT	$C\mathit{H}{=}CH{-}CO_2CH_3$
	5.5—6.0	3H m+d	$C\mathit{H}{=}C\mathit{H}{-}$, $={C}\mathit{H}{-}CO_2CH_3$
	3.7	3H s	$CO_2C\mathit{H}_3$
	0.9—2.6	remaining H	

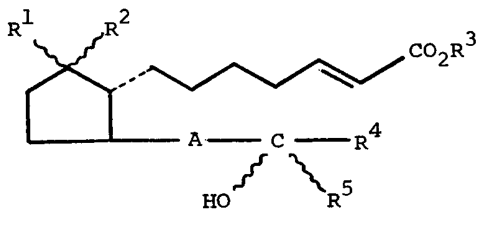
e) 7 - [2 - (3 - hydroxy - 3 - methyl - 1 - *trans* - octenyl) - 5 - oxocyclopentyl] - 2 - *trans* - heptenoic acid

was obtained by saponification of the ester prepared according to d). 160 mg of this ester were dissolved in 10 ml of DME, 1 ml of 1N NaOH and 1 ml of water were added, and the batch was left to stand overnight. It was then poured onto ice water, acidified with 1N HCl until a pH of ~1 was obtained, and the solution so prepared was extracted several times with chloroform. The united chloroform extracts were dried and evaporated. The residue was subjected to chromatography on silica gel with cyclohexane/acetic acid ester/glacial acetic acid as diluent. 101 mg of the desired final product were obtained.

NMR:	6.7—7.4	1H dT	$-C\mathit{H}{=}CH{-}CO_2H$
	5.1—6.0	5H D+	$={C}\mathit{H}{-}CO_2\mathit{H}$, $-C\mathit{H}{=}C\mathit{H}{-}$,
	2 multiplets	O*H*	

WHAT WE CLAIM IS:—

1. A compound of the general formula I



I

wherein

R¹ and R² together represent an oxygen atom or one represents a hydrogen atom and the other a hydroxyl group;

R³ represents a hydrogen atom or a linear or branched, saturated or unsaturated aliphatic or cycloaliphatic radical having up to 8 carbon atoms, or an araliphatic radical having from 7 to 9 carbon atoms;

R⁴ represents a linear or branched, saturated or unsaturated aliphatic hydrocarbon radical having up to 10 carbon atoms, or a cycloaliphatic radical having from 3 to 7 carbon atoms, each of the cited radicals optionally being substituted by any one or more of the following:

a) a linear or branched alkylthio or alkenylthio radical having up to 7 carbon atoms or, when R^5 is not a hydrogen atom and/or A is a $—CH_2—CH_2—$ group and/or one of R^1 and R^2 represents a hydrogen atom and the other represents a hydroxyl group, a linear or branched alkoxy or alkenyloxy radical having up to 7 carbon atoms,

b) a phenoxy radical optionally mono- or di-substituted by one or two substituents selected from optionally halogen-substituted alkyl groups having from 1 to 3 carbon atoms, halogen atoms, optionally halogen-substituted phenoxy radicals and alkoxy radicals having from 1 to 4 carbon atoms; the substituents being identical or different in case of disubstitution,

c) a furyloxy, thienyloxy or benzyloxy radical, each of which is optionally mono- or disubstituted in the ring by one or two substituents selected from optionally halogen-substituted alkyl groups having from 1 to 3 carbon atoms, halogen atoms and alkoxy groups having from 1 to 4 carbon atoms, the substituents being identical or different in case of disubstitution;

d) one or two fluorine atoms, a trifluoromethyl or pentafluoroethyl group,

e) a cycloalkyl radical having from 3 to 7 carbon atoms,

f) a phenyl, thienyl or furyl radical, each of which is optionally mono- or disubstituted by one or two substituents selected from optionally halogen-substituted alkyl groups having from 1 to 3 carbon atoms, halogen atoms and alkoxy groups having from 1 to 4 carbon atoms, the substituents being identical or different in case of disubstitution;

A represents a *trans* $—CH=CH—$ group or a $—CH_2—CH_2—$ group; and

R^5 represents a hydrogen atom, an alkyl group having from 1 to 5 carbon atoms, or an alkenyl or alkynyl group having from 2 to 5 carbon atoms with the proviso that when A represents a $—CH_2—CH_2$ group, R^5 is either a hydrogen atom or an alkyl group.

2. A compound as claimed in claim 1, wherein R_3 represents a hydrogen atom, a linear or branched alkyl radical having from 1 to 8 carbon atoms, a linear or branched alkenyl radical having from 2 to 4 carbon atoms, a cycloalkyl radical having from 5 to 7 carbon atoms, or an aralkyl radical having 7 or 8 carbon atoms.

3. A compound as claimed in claim 2, wherein R^3 represents a hydrogen atom, a linear alkyl radical having from 1 to 6 carbon atoms, a branched alkyl radical having from 3 to 5 carbon atoms, a linear alkenyl radical having from 2 to 4 carbon atoms, a cyclopentyl, cyclohexyl, benzyl, phenethyl or methoxybenzyl radical.

4. A compound as claimed in any one of claims 1 to 3, wherein R^4 represents a linear or branched, saturated or unsaturated aliphatic hydrocarbon radical having from 1 to 8 carbon atoms, or a cycloaliphatic hydrocarbon radical having from 5 to 7 carbon atoms, each of the cited radicals optionally being substituted by

a) a linear or branched alkoxy, alkylthio, alkenyloxy or alkenylthio radical having from 1 to 5 carbon atoms,

b) a phenoxy radical optionally mono- or disubstituted by one or two substituents selected from alkyl groups having from 1 to 3 carbon atoms, trifluoromethyl groups, halogen atoms, optionally halogen-substituted phenoxy radicals methoxy and ethoxy radicals, the substituents being identical or different in case of disubstitution,

c) a thienyloxy or benzyloxy radical optionally mono- or disubstituted in the ring by one or two substituents selected from alkyl groups having from 1 to 3 carbon atoms, trifluoromethyl groups, halogen atoms, and methoxy and ethoxy groups, the substituents being identical or different in case of disubstitution,

d) one or two fluorine atoms or a trifluoromethyl group,

e) a cycloalkyl radical having from 5 to 7 carbon atoms,

f) a phenyl or thienyl radical optionally substituted by one or two substituents selected from alkyl radicals having from 1 to 3 carbon atoms, trifluoromethyl groups, halogen atoms, methoxy and ethoxy groups, the substituents being identical or different in case of disubstitution.

5. A compound as claimed in claim 4, wherein R^4 represents a linear or branched alkyl radical having from 1 to 6 carbon atoms, a linear or branched alkenyl radical having from 3 to 5 carbon atoms or a cycloalkyl radical having from 5 to 7 carbon atoms, each of the cited radicals optionally being substituted by

a) a linear or branched alkoxy, alkylthio, alkenyloxy or alkenylthio radical having from 1 to 4 carbon atoms,

b) a phenoxy radical optionally mono- or disubstituted by one or two substituents selected from methyl, trifluoromethyl and methoxy groups, chlorine and fluorine atoms, and a phenoxy radical optionally substituted by one or more chlorine and/or fluorine atoms, the substituents being identical or different in case of disubstitution,

c) a thienyloxy or benzyloxy radical optionally mono- or disubstituted in the ring by one or two substituents selected from methyl, -trifluoromethyl and methoxy groups, the substituents being identical or different in case of disubstitution,

d) one or two fluorine atoms or a trifluoromethyl group,

e) a cycloalkyl radical having from 5 to 7 carbon atoms,

f) a phenyl or thienyl radical optionally mono- or disubstituted by substituents selected from methyl, trifluoromethyl and methoxy groups, and chlorine and fluorine atoms, the substituents being identical or different in case of disubstitution.

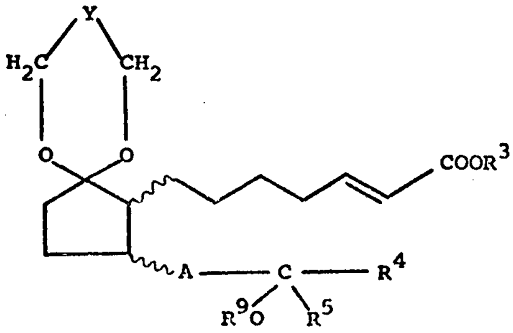
6. A compound as claimed in any one of claims 1 to 5, wherein R^5 represents an alkyl group having from 1 to 5 carbon atoms, or an alkenyl or alkynyl group having from 2 to 4 carbon atoms.

7. A compound as claimed in claim 1, and which is described in any one of Examples 15 to 18.

8. A salt of a compound as claimed in any one of claims 1 to 7.

9. A physiologically tolerable salt of a compound as claimed in any one of claims 1 to 7.

10. A process for the manufacture of a compound of the formula I as claimed in claim 1 or a salt thereof, which comprises removing by acidic hydrolysis the ketal protecting group from a compound of the formula XVII



XVII

wherein R^3, R^4, R^5 and A are as defined for formula I as claimed in claim 1, R^9 is a hydrogen atom or a protecting group which can be split off under acid conditions, and Y is a single bond, a CH_2 or a

$$\begin{array}{c} CH_3 \\ | \\ -C- \\ | \\ CH_3 \end{array}$$

group, and, when R^9 does not represent a hydrogen atom, simultaneously or previously removing the protecting group R^9, and if desired, carrying out any one or more of the following steps, in any order,

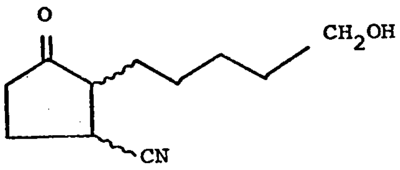
(i) esterifying the resulting compound of formula I wherein R^1 and R^2 together represents an oxygen atom, R^3 is a hydrogen atom and R^4, R^5 and A is as defined in claim 1,

(ii) reducing a resulting compound of formula I, wherein R^1 and R^2 together represent an oxygen atom and R^3, R^4, R^5 and A are as defined in claim 1, to give a compound of formula I, wherein one of R^1 and R^2 represents a hydrogen atom and the other a hydroxyl group, and

(iii) converting a compound of formula I wherein R^3 is a hydrogen atom and R^1, R^2, R^4, R^5 and A are as defined in claim 1, to a salt thereof.

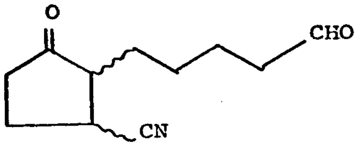
11. A process for the manufacture of a compound of formula I as claimed in claim 1 or a salt thereof, which comprises

a) oxidizing an alcohol of the formula II



II

to form an aldehyde of the formula III

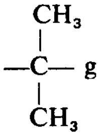


III

b) selectively converting the aldehyde of formula III with a dithiol of the formula IV

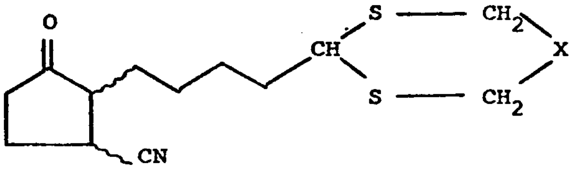
$$HS—CH_2—X—CH_2—SH \qquad IV$$

wherein X is a single bond, a CH_2 group or a



$$—C(CH_3)_2— \text{ group,}$$

in the presence of an acidic catalyst, to a dithioacetal of the formula V



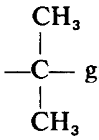
V

wherein X is as defined for formula IV,

c) reacting the dithioacetal of formula V with a diol of the formula VI

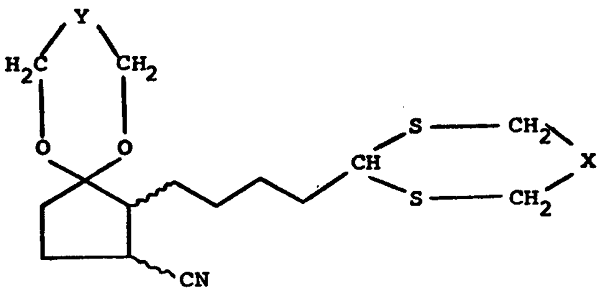
$$HO—H_2C—Y—CH_2—OH \qquad VI$$

wherein Y is a single bond, a CH_2 group or a



$$—C(CH_3)_2— \text{ group,}$$

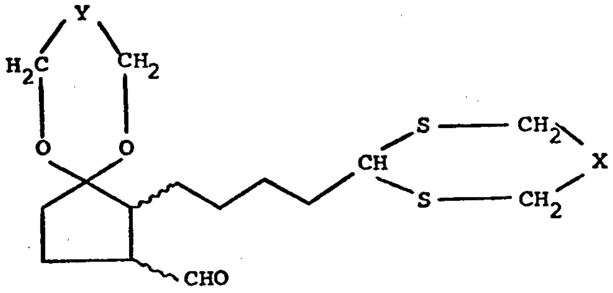
in the presence of an acidic catalyst, to form a ketal of the formula VII



VII

wherein X is as defined for formula IV and Y is as defined for formula VI,

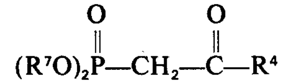
d) reducing the nitrile of formula VII to an aldehyde of the formula VIII



VIII

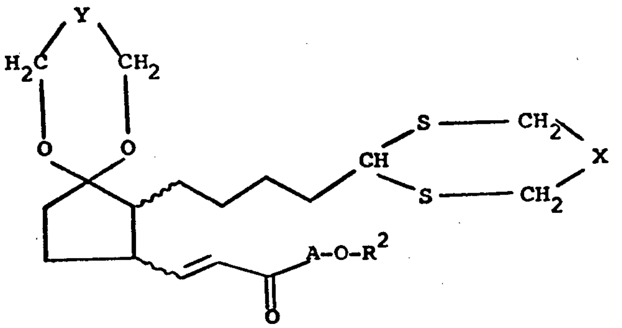
wherein X is as defined for formula IV and Y is as defined for formula VI,

e) reacting the aldehyde of formula VIII with a phosphonate of the formula IX



$$(R^7O)_2\overset{\overset{O}{\|}}{P}-CH_2-\overset{\overset{O}{\|}}{C}-R^4 \qquad IX$$

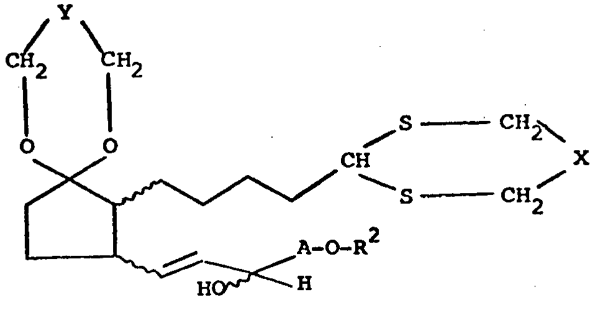
wherein R^4 is as defined for formula I in claim 1, and R^7 is a linear alkyl radical having from 1 to 4 carbon atoms, to form an unsaturated ketone of the formula X



X

wherein X is as defined for formula IV and Y is as defined for formula VI,

f) reducing the unsaturated ketone of formula X to an alcohol of the formula XI



XI

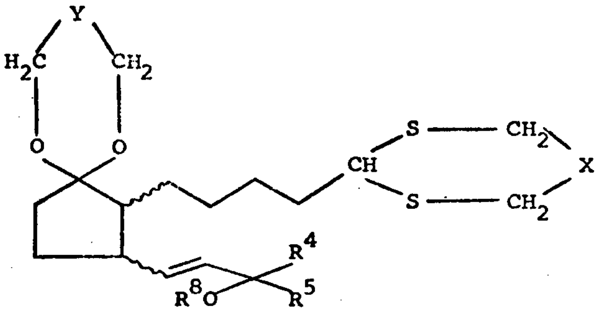
wherein R^4 is as defined for formula I, X is as defined for formula IV and Y is as defined for formula VI, and R^5 is a hydrogen atom, or

g) reacting the unsaturated ketone of formula X with an organo-metallic compound of the formula XII

$$R^5—Me \qquad XII$$

wherein R^5 is an alkyl group having from 1 to 5 carbon atoms or an alkenyl or alkynyl group having from 2 to 5 carbon atoms and Me is an alkali metal or HalMg, (Hal being chlorine, bromine or iodine) to form a compound of formula XI, wherein R^4 is as defined for formula IX, R^5 is as defined for formula XII, X is as defined for formula IV and Y is as defined for formula VI,

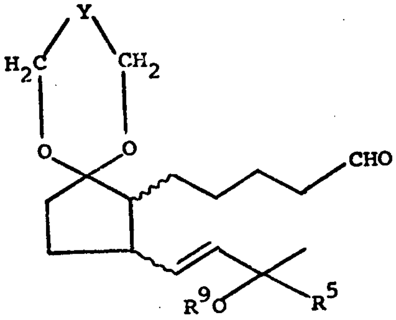
h) protecting the hydroxy group of the compound of formula XI by means of a group which can be split off under acidic conditions, thus forming a compound of the formula XIII



XIII

wherein R^4 and R^5 are as defined for formula I in claim 1, X is as defined for formula IV, Y is as defined for formula VI, and R^8 is a protecting group which can be split off under acidic conditions,

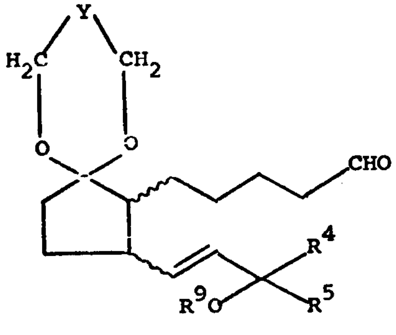
j) splitting off the thioacetal group of the compound of formula XI or XIII in a mixture of an organic solvent and water in the presence of a salt of a heavy metal or an alkyl halide, thus forming an aldehyde of the formula XIV



XIV

wherein R^4 and R^5 are as defined for formula I in claim 1, Y is as defined for formula VI, and R^9 is a hydrogen atom or a protecting group which can be split off under acid conditions,

j') optionally hydrogenating the aldehyde of formula XIV so obtained to a compound of the formula XV



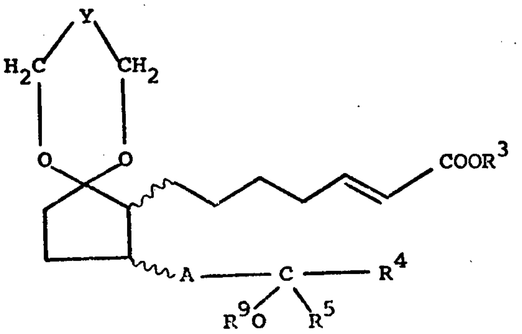
XV

wherein R^4 is as defined for formula I in claim 1, R^9 is as defined for formula XIV, Y is as defined for formula VI and R^5 is a hydrogen atom or an alkyl group having from 1 to 5 carbon atoms, in the presence of a suitable catalyst,

k) reacting a compound of formulae XIV or XV, with an ylide of the formula XVI

$$(R^{10})_3P{=}CH{-}CO_2R^3 \qquad \text{XVI}$$

wherein the radicals R^{10}, which may be identical or different, each represents a linear alkyl group having from 1 to 4 carbon atoms or a phenyl group and R^3 is as defined for formula I, in claim 1, to form a compound of the formula XVII



XVII

wherein R^3, R^4, R^5 and A are as defined for formula I in claim 1, R^9 is as defined for formula XV and Y is as defined for formula VI.

l) optionally preparing a compound of the formula XVII wherein R^9 is hydrogen, from the corresponding compound of formula XVII wherein R^9 is a protecting group which can be split off under acidic conditions, by means of mild acidic hydrolysis,

m) removing the ketal protecting group from the compound of formula XVII by means of acidic hydrolysis and, in the case where R^9 is not a hydrogen atom simultaneously or previously also removing the protecting group R^9, thus obtaining a compound of formula I, wherein R^1 and R^2 together are oxygen and R^3, R^4, R^5 and A are as defined for formula I, as claimed in claim 1 and, if desired, carrying out any one or more of the following steps, in any order

n) esterifying a compound of formula I, wherein R^1 and R^2 to gether are oxygen, R^3 is hydrogen and R^4, R^5 and A are as defined in claim 1, to form a compound of formula I, wherein R^1 and R^2 together are oxygen, R^3 is a linear or branched, saturated or unsaturated aliphatic or cycloaliphatic radical having from 1 to 8 carbon atoms or an araliphatic radical having from 7 to 9 carbon atoms, and R^4, R^5 and A are as defined in claim 1, and

o) reducing a compound of formula I, wherein R^1 and R^2 together are oxygen and R^3, R^4, R^5 and A are as defined for formula I as claimed in claim 1, to the corresponding compound of formula I, wherein one of R^1 and R^2 represents a hydrogen atom and the other a hydroxyl group, and R^3, R^4, R^5 and A are as defined in claim 1, and

p) converting a compound of formula I, wherein R^3 is hydrogen and R^1, R^2, R^4, R^5 and A are as defined in claim 1, into a salt thereof.

12. A process as claimed in claim 10 carried out substantially as described in any one of Examples 15 to 18 herein.

13. A process as claimed in claim 11, carried out substantially as described in any one of the Examples 6 to 18 herein.

14. A compound as claimed in claim 1, whenever produced by a process as claimed in any one of claims 10 to 13.

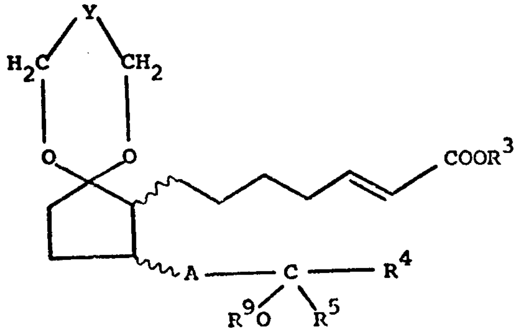
15. A pharmaceutical preparation which comprises a compound as claimed in any one of claims 1 to 7 or claim 14, or a physiologically tolerable salt thereof as active ingredient, in admixture or conjunction with a pharmaceutically suitable carrier.

16. A pharmaceutical preparation as claimed in claim 15, in unit dosage form.

17. A pharmaceutical preparation as claimed in claim 16, which comprises from 0.05 to 200 mg of the active ingredient per unit dose.

18. A pharmaceutical preparation as claimed in any one of claims 15 to 17, which comprises one or more further active substances. wherein Y is as defined for formula VII, R^4 is as defined for formula I, R^9 is as defined for formula XIV and R^5 is alkyl having from 1 to 5 carbon atoms.

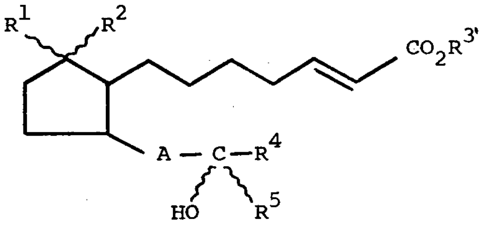
19. Compounds of the formula XVII



XVII

wherein R^3, R^4, R^5 and A are as defined in claim 1, and R^9 and Y are as defined in claim 10.

20. A compound of the general formula Ia



Ia

in which R^1 to R^5 and A are as defined in claim 1.

ABEL & IMRAY,
Chartered Patent Agents,
Northumberland House,
303—306 High Holborn,
London, WC1V 7LH.

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