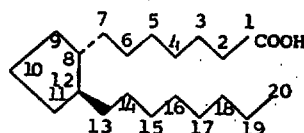


SPECIFICATION Prostaglandin analogues

This invention is concerned with new prostaglandin analogues.
Prostaglandins are derivatives of prostanic acid which has the following formula:



Various types of prostaglandins are known, the types depending *inter alia* on the structure and substituents on the alicyclic ring. For example, the alicyclic ring of prostaglandin E(PGE) has the structure:



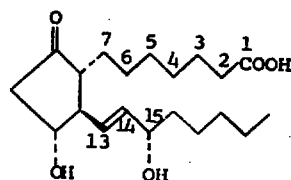
The dotted lines in the foregoing formulae and in other formulae throughout this specification denote, in accordance with generally accepted rules of nomenclature, that the attached grouping lies behind the general-plane of the ring system, i.e. that the grouping is in α -configuration, the thickened lines

denote that the grouping lies in front of the general plane of the system, i.e. that the grouping is in β -configuration, and the wavy line



indicates that the grouping is in α - or β -configuration.

Such compounds are sub-classified according to the position of double bond(s) in the side chain(s) attached to the 8- and 12-positions of the alicyclic ring. Thus PG₁ compounds have a *trans*-double bond between C₁₃—C₁₄ (*trans*- Δ^{13}) and PG₂ compounds have a *cis*-double bond between C₅—C₆ and a *trans*-double bond between C₁₃—C₁₄ (*cis*- Δ^5 , *trans*- Δ^{13}). For example, prostaglandin E₁ (PGE₁) is characterised by the following structure III.



The structure of PGE₂, as a member of the PG₂ group, corresponds to that of formula III with a *cis*-double bond between the carbon atoms in positions 5 and 6. Compounds in which the double bond between the carbon atoms in positions 13 and 14 of members of the PG₁ group is replaced by ethylene are known as dihydroprostaglandins, e.g. dihydro-prostaglandin-E₁ (dihydro-PGE₁).

Moreover, when one or more methylene groups are eliminated from the aliphatic group attached to the 12-position of the alicyclic ring of the prostaglandins the compounds are known, in accordance with the usual rules of organic nomenclature, as nor-prostaglandins and, when more than one methylene group is eliminated, the number is indicated by di-, tri- etc. before the prefix "nor".

Prostaglandins are generally known to possess pharmacological properties, for example they stimulate smooth muscle, have hypotensive, diuretic, bronchodilating and antilipolytic activities, and also inhibit blood platelet aggregation and gastric acid secretion, and are, accordingly, useful in the treatment of hypertension, thrombosis, asthma and gastro-intestinal ulcers, in the induction of labour and abortion in pregnant female mammals, in the prevention of arteriosclerosis, and as diuretic agents.

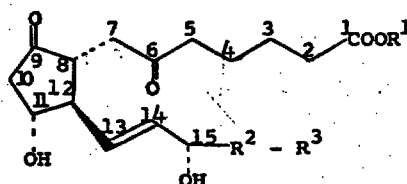
They are fat-soluble substances obtainable in very small quantities from various tissues of animals which secrete the prostaglandins in the living body.

For example, PGE's have an inhibiting effect on gastric acid secretion and may, accordingly, be used in the treatment of gastric ulcers. They also inhibit the release of free fatty acid induced by

epinephrine and as a result they reduce the concentration of free fatty acid in blood, and are, accordingly, useful in the prevention of arteriosclerosis and hyperlipemia. PGE₁ inhibits blood platelet aggregation and also removes the thrombus and prevents thrombosis. PGE's have a stimulating effect on smooth muscle and increase the intestinal peristalsis; these actions indicate therapeutic utility on post-operative ileus and as purgatives. PGE's may also be used as oxytocics, as abortifacients in the first and second trimesters; in the post-labour abortion of the placenta, and as oral contraceptives because they regulate the sexual cycle of female mammals. PGE's have vasodilator and diuretic activities. They are useful for improvement in patients suffering from cerebral vascular disease because they increase the cerebral blood flow, and are also useful in the treatment of asthmatic conditions in patients because of their bronchodilating activity.

During the past decade widespread investigations have been carried out in order to discover *inter alia* new products possessing the pharmacological properties of the 'natural' prostaglandins or one or more of such properties to an enhanced degree, or hitherto unknown pharmacological properties. It has now been found, after research and experimentation, that certain 6-oxo-17,20-dimethyl prostaglandin E₁ compounds possess the pharmacological properties of the 'natural' prostaglandins and are, in some aspects of their activities, an improvement, for example possessing an enhanced strength of activity and/or a prolonged duration of activity.

The present invention accordingly provides the 6-oxo-17,20-dimethyl prostaglandin E₁ analogues of the general formula:

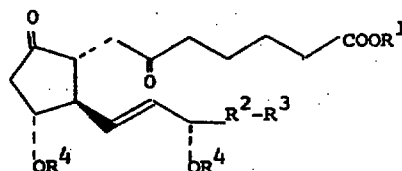


IV

[wherein R¹ represents a hydrogen atom or a straight- or branched chain alkyl group containing from 1 to 4 carbon atoms, the grouping —R²—R³ represents a 2-methylhexyl group and the dotted line attached to the C—11 and C—15 carbon atoms represents α -configuration (i.e. *S*-configuration)] and cyclodextrin clathrates of such acids and esters and, when R¹ represents a hydrogen atom, non-toxic (e.g. sodium) salts thereof. It is to be understood that the C13—C14 double bond in formula IV and the corresponding double bonds in other formulae in this specification and the accompanying claims are all *trans*.

Examples of the straight- or branched- chain alkyl group containing from 1 to 4 carbon atoms represented by R¹ are methyl, ethyl, propyl and butyl and their isomers. Preferably R¹ represents a hydrogen atom or a methyl group.

According to a feature of the present invention, the prostaglandin E₁ and analogues of general formula IV, wherein the various symbols are as hereinbefore defined, may be prepared by the hydrolysis to hydroxy groups of the groups OR⁴ of a compound of the general formula:



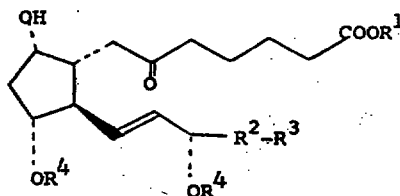
V

wherein R⁴ represents a tetrahydropyran-2-yl or tetrahydrofuran-2-yl group, each such group being unsubstituted or substituted by at least one alkyl group, or represents a 1-ethoxyethyl group, and the other symbols are as hereinbefore defined.

The groups OR⁴ of the compounds of general formula V may be converted to hydroxy groups by mild acidic hydrolysis (1) with an aqueous solution of an organic acid such as acetic acid, propionic acid, oxalic acid or *p*-toluenesulphonic acid, or an aqueous solution of an inorganic acid, such as hydrochloric acid or sulphuric acid, advantageously in the presence of an inert solvent miscible with water, e.g. a lower alkanol such as methanol or ethanol (preferably methanol), or an ether such as 1,2-dimethoxyethane, dioxan or tetrahydrofuran (preferably tetrahydrofuran), at a temperature ranging from ambient to 75°C (preferably at a temperature below 45°C), or (2) with an anhydrous solution of an organic acid such as *p*-toluenesulphonic acid or trifluoroacetic acid in a lower alkanol such as methanol or ethanol at a temperature ranging from 10° to 45°C. Advantageously the mild hydrolysis may be

carried out with a mixture of hydrochloric acid, water and tetrahydrofuran, a mixture of hydrochloric acid, water and methanol, a mixture of acetic acid, water and tetrahydrofuran, or a mixture of *p*-toluenesulphonic acid and methanol.

Compounds of general formula V may be prepared by the oxidation of a compound of the general formula:

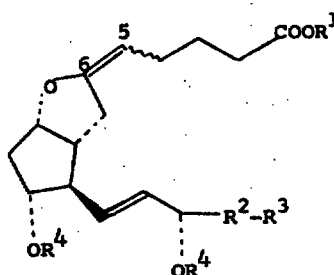


VI

(wherein the various symbols are as hereinbefore defined), by methods known *per se* for the conversion of a hydroxy group in the 9-position of a prostaglandin compound to an oxo group. By the expression "methods known *per se*" as used in this specification is meant methods heretofore used or described in the chemical literature.

Preferably the oxidation is carried out under mild, neutral conditions, for example, by reaction with (1) dimethyl sulphide-*N*-chlorosuccinimide complex, thioanisole-*N*-chlorosuccinimide complex, dimethyl sulphide-chlorine complex or thioanisole-chlorine complex in a haloalkane, e.g. chloroform, methylene chloride or carbon tetrachloride, or toluene at a temperature of from -30°C to 0°C [cf. J. Amer. Chem. Soc., 94, 7586 (1972)], (2) chromium trioxide-pyridine complex, e.g. Collins' reagent, in a haloalkane, e.g. chloroform, methylene chloride or carbon tetrachloride, at a temperature of from 0°C to ambient, preferably at 0°C , or (3) Jones's reagent in the presence of acetone and dilute sulphuric acid at a temperature of from 0°C to ambient.

Compounds of general formula VI, wherein the various symbols are as hereinbefore defined may be prepared by hydrolysis under acidic conditions of a compound of the general formula:

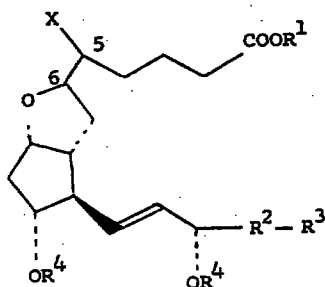


VII

wherein the wavy line $\sim$ attached to the carbon atom in position 5 indicates that the double bond between C_5-C_6 is *Z* or *E* and the other symbols are as hereinbefore defined.

The hydrolysis must be carried out carefully to avoid the elimination of the group R^4 , and may be carried out with an aqueous solution of an organic acid, e.g. acetic acid, propionic acid, oxalic acid or *p*-toluenesulphonic acid, or an aqueous solution of an inorganic acid, e.g. hydrochloric or sulphuric acid, in the presence or absence of an inert organic solvent miscible with water, e.g. an ether such as 1,2-dimethoxyethane, dioxan or tetrahydrofuran (preferably tetrahydrofuran), at a temperature of from 0° to 75°C (preferably from 0° to ambient). Advantageously the hydrolysis may be carried out with a mixture of acetic acid, water and tetrahydrofuran, a mixture of dilute hydrochloric acid and tetrahydrofuran, or dilute hydrochloric acid. The progress of the hydrolysis is preferably monitored by thin layer chromatography to avoid elimination of the groups R^4 .

Compounds of general formula VII are prepared by dehydrohalogenation of a compound of the general formula:

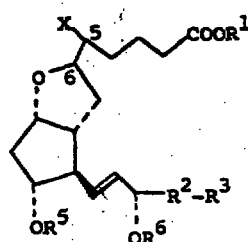


VIII 35

wherein X represents a bromine or iodine atom, the absolute configurations of C₅ and C₆ are (5S, 6S), (5R, 6R), (5S, 6R), or (5R, 6S), or a mixture thereof, and the other symbols are as hereinbefore defined.

- The dehydrohalogenation may be carried out with a known dehydrohalogenation reagent, for example (1) when X represents a bromine atom, a bicycloamine such as DBU (i.e. 1,5-diazabicyclo[5.4.0]undecane-5), DBN (i.e. 1,5-diazabicyclo[4.3.0]nonene-5) or DABCO (i.e. 1,4-diazabicyclo[2.2.2]octane), or an alkali metal, e.g. sodium or potassium, alcoholate containing from 1 to 4 carbon atoms, or (2) when X represents an iodine atom, a bicycloamine such as DBN, DBU or DABCO, or an alkali metal, e.g. sodium or potassium, alcoholate containing from 1 to 4 carbon atoms, superoxide, carbonate, hydroxide, benzoate, acetate, trifluoroacetate or bicarbonate, or silver acetate, or tetramethylammonium superoxide. The reaction may be carried out at a temperature from ambient to 110°C, preferably at a temperature from ambient to 80°C, and (1) when the reagent is a bicycloamine, optionally in the presence of an inert organic solvent, preferably in the absence of an inert organic solvent or in the presence of toluene or benzene, or (2) when the reagent is other than a bicycloamine, in the presence of an inert organic solvent, e.g. an alkanol containing from 1 to 4 carbon atoms, such as methanol or ethanol, or *N,N*-dimethylformamide.

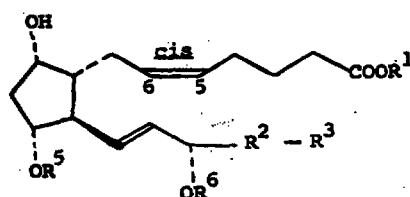
Compounds of general formula VIII may be prepared from a compound of the general formula:—



IX

- [wherein R⁵ and R⁶, which may be the same or different, each represents a hydrogen atom, a tetrahydropyran-2-yl or tetrahydrofuran-2-yl group, each group being unsubstituted or substituted by at least one alkyl group, or a 1-ethoxyethyl group, the absolute configurations of C₅ and C₆ are (5S, 6S), (5R, 6R), (5S, 6R) or (5R, 6S) or a mixture thereof and, the other symbols are as hereinbefore defined], when one or both of the symbols R⁵ and R⁶ represents hydrogen, by reaction of the compound of general formula IX with a 2,3-dihydropyran, 2,3-dihydrofuran or ethyl vinyl ether in an inert organic solvent, e.g. methylene chloride, in the presence of a condensing agent, e.g. *p*-toluenesulphonic acid. It will be appreciated that compounds of general formula VIII fall within the scope of general formula IX when R⁵ and R⁶ both represent a tetrahydropyran-2-yl or tetrahydrofuran-2-yl group, each such group being unsubstituted or substituted by at least one alkyl group, or a 1-ethoxyethyl group.

- Compounds of general formula IX, wherein the absolute configurations at C₅ and C₆ are (5R, 6R) or (5S, 6S) or a mixture thereof and the other symbols are as hereinbefore defined, may be prepared by bromination or iodination, and simultaneous cyclisation of a compound of the general formula:

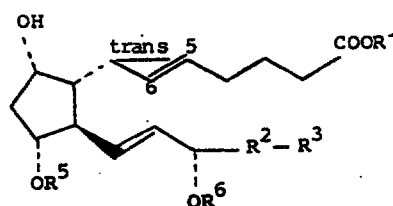


X

wherein the double bond between C₅—C₆ is *cis* and the various symbols are as hereinbefore defined.

- The conversion of a compound of general formula X to a compound of general formula IX may be suitably carried out, (1) when X in the compound of general formula IX represents a bromine atom, with *N*-bromosuccinimide or *N*-bromoacetamide in an aprotic organic solvent, e.g. methylene chloride, chloroform, carbon tetrachloride, diethyl ether, *N,N*-dimethylformamide or tetrahydrofuran, or a mixture of two or more of them, at a temperature of from -30° to 70°C, or (2) when X in the compound of general formula IX represents an iodine atom, with (i) iodine in pyridine, (ii) potassium periodate and potassium iodide in aqueous acetic acid, (iii) iodine and potassium iodide in the presence of an alkali metal, e.g. sodium or potassium, carbonate or bicarbonate in water, or (iv) iodine in the presence of an alkali metal, e.g. sodium or potassium, carbonate in an inert organic solvent, e.g. methylene chloride or chloroform, at a temperature of from 0°C to ambient. The product of general formula IX, thus obtained, is a mixture of isomers in which the absolute configurations of C₅ and C₆ are (5R, 6R) and (5S, 6S). If desired, the mixture may be separated by column, thin layer or high-speed liquid chromatography on silica gel to give each of the isomers, although such separation is not required.

Compounds of general formula IX, wherein the absolute configuration at C₅ and C₆ are (5R, 6S) or (5S, 6R) or a mixture thereof and the various symbols are as hereinbefore defined, may be prepared from a compound of the general formula:—

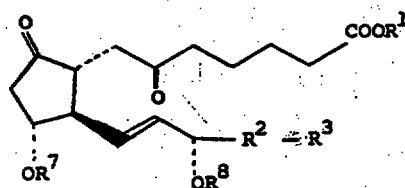


XI

(wherein the double bond between C₅—C₆ is *trans* and the various symbols are as hereinbefore defined) by means heretofore mentioned for the conversion of compounds of general formula X to those of general formula IX. The product of general formula IX, thus obtained, is a mixture of isomers in which the absolute configurations of C₅ and C₆ are (5*R*, 6*S*) and (5*S*, 6*R*). If desired, the mixture may be separated by column, thin layer or high-speed liquid chromatography on silica gel to give each of the isomers, although such separation is not required.

Compounds of general formula XI may be prepared by photoisomerization of compounds of general formula X with light from a high pressure mercury lamp in the presence of diphenyl sulphide or diphenyl sulphide in an inert organic solvent, e.g. a mixture of benzene and methanol, at room temperature. The product obtained may be purified by column or thin layer chromatography on silica gel pretreated with silver nitrate to give compounds of general formula XI.

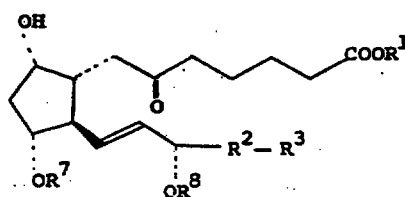
According to a further feature of the present invention, the prostaglandin E₁ analogues of general formula IV, wherein the various symbols are as hereinbefore defined, may also be prepared by the hydrolysis to hydroxy groups of the groups —OR⁷ and —OR⁸ of a compound of the general formula:



XII

(wherein R⁷ and R⁸, which may be the same or different, each represent a tetrahydropyran-2-yl or tetrahydrofuran-2-yl group, each group being unsubstituted or substituted by at least one alkyl group, a 1-ethoxyethyl group, or a trimethylsilyl group, with the proviso that at least one of the symbols R⁷ and R⁸ represents a trimethylsilyl group, and the other symbols are as hereinbefore defined) by means heretofore mentioned for the conversion of compounds of general formula V to those of general formula IV.

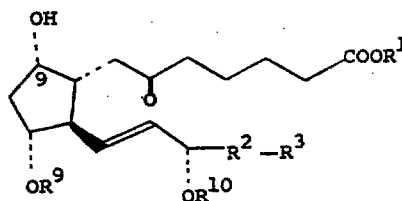
Compounds of general formula XII may be prepared from a compound of the general formula:



XIII

(wherein the various symbols are as hereinbefore defined) by means heretofore mentioned for the conversion of compounds of general formula VI to those of general formula V.

Compounds of general formula XIII may be prepared from a compound of the general formula:—



XIV

(wherein R⁹ and R¹⁰, which may be the same or different, each represent a hydrogen atom, a tetrahydropyran-2-yl or tetrahydrofuran-2-yl group, each such group being unsubstituted or substituted by at least one alkyl group, or a 1-ethoxyethyl group with the proviso that at least one of the symbols R⁹ and R¹⁰ represents a hydrogen atom, and the other symbols are as hereinbefore defined) by reaction with a suitable trimethylsilylating reagent, e.g. *N*-trimethylsilyldiethylamine or *N*,*O*-bis(trimethylsilyl)acetamide, in an inert organic solvent, e.g. acetone or methylene chloride, preferably at room temperature.

Compounds of general formula XIV, wherein the various symbols are as hereinbefore defined, may be prepared from a compound of general formula IX, wherein at least one of the symbols R⁵ and R⁶ represents a hydrogen atom, by means heretofore mentioned for the conversion of compounds of general formula VIII to those of general formula VI via compounds of general formula VII.

If desired, the compounds of general formula IX or X, wherein R¹ is other than a hydrogen atom and the other symbols are as hereinbefore defined, may be prepared by esterification of a compound of general formula IX or X, wherein R¹ is a hydrogen atom and the other symbols are as hereinbefore defined, by methods known *per se* for the esterification of carboxylic acids, for example, by reaction with (i) the appropriate diazoalkane, e.g. diazomethane, in an inert organic solvent, e.g. diethyl ether, at a temperature of from -10° to 25°C and preferably 0°C, (ii) the appropriate alcohol in the presence of dicyclohexylcarbodiimide as condensing agent, or (iii) the appropriate alcohol following the formation of a mixed acid anhydride by adding a tertiary amine and then a pivaloyl halide or an arylsulphonyl or alkylsulphonyl halide (cf. our British Patents Nos. 1362956 and 1364125).

If desired, the acids of general formula VI, VII, VIII or IX, wherein R¹ represents a hydrogen atom, and the other symbols are as hereinbefore defined, may be prepared from the corresponding esters of general formula VI, VII, VIII or IX wherein R¹ is other than a hydrogen atom, and the other symbols are as defined, by alkaline hydrolysis with an aqueous solution of an alkali metal, e.g. sodium or potassium, hydroxide or carbonate in the presence of an inert organic solvent miscible with water, e.g. a lower alkanol such as methanol or ethanol, preferably at ambient temperature.

Starting materials of general formula X may be prepared by the methods described in Japanese Patent Kokai Nos. 49—124048, 49—134656, 50—13362, 50—25549, 50—101340 and 51—68547, British Patent Specification Nos. 1398291 and 1483240, and United States Patent Specification No. 4024174, or obvious modifications of these methods.

According to a further feature of the present invention the prostaglandin E₁ analogues of general formula IV wherein R¹ represents an alkyl group may be prepared by esterification of the corresponding acid of general formula IV wherein R¹ represents a hydrogen atom by methods known *per se* for example by reaction with (i) the appropriate diazoalkane in an inert organic solvent, e.g. diethyl ether, at a temperature of from -0° to 25°C and preferably 0°C, (ii) the appropriate alcohol in the presence of dicyclohexylcarbodiimide as condensing agent, or (iii) the appropriate alcohol following formation of a mixed anhydride by adding a tertiary amine and pivaloyl halide or an alkyl sulphonyl or arylsulphonyl halide (cf. our British Patents Nos. 1362956 and 1364125).

Cyclodextrin clathrates of the prostaglandin analogues of general formula IV may be prepared by dissolving the cyclodextrin in water or an organic solvent which is miscible with water and adding to the solution the prostaglandin analogue in a water-miscible organic solvent. The mixture is then heated and the desired cyclodextrin clathrate product isolated by concentrating the mixture under reduced pressure or by cooling and separating the product by filtration or decantation. The ratio of organic solvent to water may be varied according to the solubilities of the starting materials and products. Preferably the temperature is not allowed to exceed 70°C during the preparation of the cyclodextrin clathrates. α -, β - or γ -Cyclodextrins or mixtures thereof may be used in the preparation of the cyclodextrin clathrates.

Conversion into their cyclodextrin clathrates serves to increase the stability of the prostaglandin analogues.

Compounds of general formula IV wherein R¹ represents a hydrogen atom may, if desired, be converted by methods known *per se* into salts. Preferably the salts are non-toxic salts. By the term "non-toxic salts", as used in this specification, is meant salts the cations of which are relatively innocuous to the animal organism when used in therapeutic doses so that the beneficial pharmacological properties of the compounds of general formula IV are not vitiated by side-effects ascribable to those cations. Preferably the salts are water-soluble. Suitable non-toxic salts include the alkali metal, e.g. sodium or potassium, salts, the alkaline earth metal, e.g. calcium or magnesium salts and ammonium salts, and pharmaceutically acceptable, (i.e. non-toxic) amine salts. Amines suitable for forming such salts with carboxylic acids are well known and include for example, amines derived in theory by the replacement of one or more of the hydrogen atoms of ammonia by groups, which may be the same or different when more than one hydrogen atom is replaced, selected from, for example, alkyl groups containing from 1 to 6 carbon atoms and hydroxyalkyl groups containing from 1 to 3 carbon atoms. Suitable non-toxic amine salts are, e.g. tetraalkylammonium, such as tetramethylammonium, salts, and other organic amine salts such as methylamine salts, dimethylamine salts, cyclopentylamine salts, benzylamine salts, phenethylamine salts, piperidine salts, monoethanolamine salts, diethanolamine salts, lysine salts or arginine salts.

Salts may be prepared from the acids of general formula IV wherein R¹ represents a hydrogen atom by methods known *per se*, for example by reaction of stoichiometric quantities of an acid of general formula IV and the appropriate base, e.g. an alkali metal or alkaline earth metal hydroxide or carbonate, ammonium hydroxide, ammonia or an organic amine, in a suitable solvent. The salts may be isolated by lyophilisation of the solution or, if sufficiently insoluble in the reaction medium, by filtration, if necessary after removal of part of the solvent.

The prostaglandin E₁ analogues of general formula IV and their cyclodextrin clathrates and, when R¹ represents a hydrogen atom, their non-toxic salts possess the valuable pharmacological properties

(15)

typical of the prostaglandins in a selective fashion, in particular hypotensive activity, inhibitory activity on blood platelet aggregation, and inhibitory activity on gastric acid secretion and gastric ulceration, and are useful in the treatment of hypertension, in the treatment of disorders of the peripheral circulation, in the prevention and treatment of cerebral thrombosis and myocardial infarction and in the treatment of

- 5 gastric ulceration. For example, in standard laboratory tests, (i) by intravenous administration to the allobarbitol-anaesthetized dog, 6-oxo-17S,20-dimethyl-PGE₁ methyl ester produces a fall in blood pressure of 32 mm Hg and 60 mm Hg lasting 8 and 11 minutes at the doses of 0.2 and 0.5 $\mu\text{g/kg}$ animal body weight, respectively. (ii) 6-oxo-17S,20-dimethyl-PGE₁ methyl ester produces a 50% inhibition of adenosine diphosphate-induced blood platelet aggregation in platelet-rich plasma of rats at the concentration of $1.8 \times 10^{-3} \mu\text{g/ml}$, in comparison with controls (iii) 6-oxo-17S,20-dimethyl-PGE₁ methyl ester produces an increase in gastric acid pH from 2.0—2.5 to at least 4.0 in 50% of pentagastrin-treated rats when perfused into the stomach at a rate of 0.44 $\mu\text{g/animal/minute}$, (iv) in stress ulceration of rats [produced according to the method of Takagi and Okabe — Jap. J. Pharmac., 18, 9—18(1968) by soaking rats in a water bath at 19°C for 6 hours]. 6-oxo-17S,20-dimethyl-PGE₁ methyl ester produces 74.06% and 61.5% inhibition of stress ulceration by oral administration at the doses of 10 and 20 $\mu\text{g/kg}$ animal body weight, respectively, and (v) in indomethacin-induced ulceration of rats, 6-oxo-17S,20-dimethyl-PGE₁ methyl ester produces 83.25% and 92.64% inhibitions of indomethacin-induced ulceration by oral administration at the doses of 5 and 10 $\mu\text{g/kg}$ animal body weight, respectively.

- 20 The prostaglandin analogues of the present invention, their cyclodextrin clathrates and non-toxic salts can cause diarrhoea, but the dose by oral administration of 6-oxo-17S,20-dimethyl-PGE₁ methyl ester required to produce diarrhoea in 50% of mice so treated is $>10 \text{ mg/kg}$ animal body weight. 6-Oxo-17S,20-dimethyl-PGE₁ methyl ester is a particularly preferred prostaglandin analogue of the invention.

- 25 Compounds of formulae V, VI, XII and XIII are new and as such constitute a feature of the present invention.

The following Reference Examples and Examples illustrate the preparation of new prostaglandin E₁ analogues of the present invention. In them, 'TLC', 'IR' and 'NMR' represent respectively 'Thin layer chromatography', 'Infrared absorption spectrum' and 'Nuclear magnetic resonance spectrum'.

- 30 Where solvent ratios are specified in chromatographic separations, the ratios are by volume.

REFERENCE EXAMPLE 1

(13E)-(5RS,6RS,9 α ,11 α ,15S)-5-Bromo-6,9-epoxy-11,15-bis(tetrahydropyran-2-yloxy)prost-13-enoic acid methyl ester

- 35 Under an atmosphere of nitrogen, a solution of 3.4 g of (5Z,13E)-(9 α ,11 α ,15S)-9-hydroxy-11,15-bis-(tetrahydropyran-2-yloxy)prosta-5,13-dienoic acid methyl ester in a mixture of 30 ml of methylene chloride and 6 ml of *N,N*-dimethylformamide was added dropwise to a suspension of 1.35 g of *N*-bromosuccinimide in 50 ml of methylene chloride at -20° to -10°C and the mixture was stirred for 30 minutes at the same temperature. The reaction mixture was then poured into ice-water and extracted with diethyl ether. The extract was washed with water and an aqueous solution of sodium chloride, dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of cyclohexane and ethyl acetate (4:1) as eluent to give 3.43 g of the title compound having the following physical characteristics:—

- 40 TLC (developing solvent, benzene:ethyl acetate = 2:1):
45 $R_f = 0.65$ and 0.69 ;
IR (liquid film): $\nu = 1745, 1440, 1030, 980 \text{ cm}^{-1}$;
NMR (CDCl_3 solution): $\delta = 5.72\text{—}5.30$ (2H, m), $4.80\text{—}4.46$ (3H, m), $4.32\text{—}2.32$ (11H, m), $1.00\text{—}0.75$ (3H, m).

The following compound was prepared by the same procedure as described above.

- 50 (a) (13E)-(5RS,6RS,9 α ,11 α ,15S,16S)-5-Bromo-6,9-epoxy-11,15-bis(tetrahydropyran-2-yloxy)-16-methylprost-13-enoic acid methyl ester, having the following physical characteristics, was prepared from (5Z,13E)-(9 α ,11 α ,15S,16S)-9-hydroxy-11,15-bis(tetrahydropyran-2-yloxy)-16-methylprosta-5,13-dienoic acid methyl ester.

TLC (developing solvent, benzene:ethyl acetate:methanol; 19:38:1):

- 55 $R_f = 0.45$ and 0.54 ;
IR (liquid film): $\nu = 1710, 1440, 1020, 980 \text{ cm}^{-1}$;
NMR (CDCl_3 solution): $\delta = 8.70$ (1H, broad s), $5.70\text{—}5.25$ (2H, m), $4.80\text{—}4.45$ (3H, m), $4.23\text{—}3.25$ (8H, m), $1.02\text{—}0.75$ (6H, m).

REFERENCE EXAMPLE 2

- 60 (13E)-(5RS,6RS,9 α ,11 α ,15S)-5-Iodo-6,9-epoxy-11,15-bis(tetrahydropyran-2-yloxy)-15-(3-propylcyclopentyl)-16,17,18,19,20-pentanorprost-13-enoic acid methyl ester

To a solution of 980 mg of (5Z,13E)-(9 α ,11 α ,15S)-9-hydroxy-11,15-bis(tetrahydropyran-2-yloxy)-15-(3-propylcyclopentyl)-16,17,18,19,20-pentanorprosta-5,13-dienoic acid methyl ester in 5 ml of methylene chloride was added a solution of 1.428 g of sodium bicarbonate in 15 ml of water and the

mixture was cooled to 0° to 5°C in an ice-bath. A solution of 0.475 g of iodine in 20 ml of methylene chloride at the same temperature was added in portions to the mixture and then the reaction mixture was stirred for 1 hour. An aqueous solution of sodium thiosulphate was added to the reaction mixture until the colour of iodine vanished. The reaction mixture was extracted with chloroform and the extract

- 5 was dried over sodium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of cyclohexane and ethyl acetate (1:1) as eluent to give 974 mg of the title compound having the following physical characteristics:—
TLC (developing solvent, cyclohexane:ethyl acetate = 2:1):
R_f = 0.60;

- 10 IR (liquid film): ν = 2950, 2875, 1742 cm⁻¹;
NMR (CDCl₃ solution): δ = 5.68—5.30 (2H, m), 4.78—4.48 (3H, m), 3.67 (3H, s), 0.98—0.76 (3H, m).

The following compounds were prepared by the same procedure as described above.

- (a) (13*E*)-(5*RS*,6*RS*,9 α ,11 α ,15*RS*)-5-iodo-6,9-epoxy-11,15-dihydroxy-15-methylprost-13-enoic acid methyl ester, having the following physical characteristics, was prepared from (5*Z*,13*E*)-(9 α ,11 α ,15*RS*)-9,11,15-trihydroxy-15-methylprosta-5,13-dienoic acid methyl ester.
15 TLC (developing solvent, ethyl acetate):
R_f = 0.45;

- IR (liquid film): ν = 2970, 2950, 2880, 1745 cm⁻¹;
NMR (CDCl₃ solution): δ = 5.82—5.3 (2H, m), 4.71—4.45 (1H, m), 4.3—3.7 (2H, m), 3.69 (3H, s).

- 20 (b) (13*E*)-(5*RS*,6*RS*,9 α ,11 α ,15*S*,17*S*)-5-iodo-6,9-epoxy-11,15-dihydroxy-17,20-dimethylprost-13-enoic acid methyl ester, having the following physical characteristics, was prepared from (5*Z*,13*E*)-(9 α ,11 α ,15*S*,17*S*)-9,11,15-trihydroxy-17,20-dimethylprosta-5,13-dienoic acid methyl ester.
TLC (developing solvent, ethyl acetate):
R_f = 0.42;

- 25 IR (liquid film): ν = 2980, 2950, 1850, 1750 cm⁻¹;
NMR (CDCl₃ solution): δ = 5.5—5.3 (2H, m), 3.54 (3H, s).

REFERENCE EXAMPLE 3

(13*E*)-(5*RS*,6*RS*,9 α ,11 α ,15*RS*)-5-iodo-6,9-epoxy-11,15-bis(tetrahydropyran-2-yloxy)-15-methylprost-13-enoic acid methyl ester

- 30 To a solution of 1.067 g of (13*E*)-(5*RS*,6*RS*,9 α ,11 α ,15*RS*)-5-iodo-6,9-epoxy-11,15-dihydroxy-15-methylprost-13-enoic acid methyl ester [prepared as described in Reference Example 2(a)] in 20 ml of methylene chloride were added 1.4 mg of *p*-toluenesulphonic acid and 1.337 g of 2,3-dihydropyran and the mixture was stirred at -4°C for 4.5 hours. The reaction mixture was then neutralised with an aqueous solution of sodium bicarbonate and extracted with chloroform. The extract was dried over
35 magnesium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of cyclohexane and ethyl acetate (2:1) as eluent to give 1.2 g of the title compound having the following physical characteristics:—
TLC (developing solvent, cyclohexane:ethyl acetate = 1:1):
R_f = 0.67;

- 40 IR (liquid film): ν = 2950, 2880, 1745 cm⁻¹;
NMR (CDCl₃ solution): δ = 5.8—5.2 (2H, m), 5.1—4.3 (3H, m), 3.67 (3H, s).

The following compound was prepared by the same procedure as described above.

- (a) (13*E*)-(5*RS*,6*RS*,9 α ,11 α ,15*S*,17*S*)-5-iodo-6,9-epoxy-11,15-bis(tetrahydropyran-2-yloxy)-17,20-dimethylprost-13-enoic acid methyl ester, having the following physical characteristics, was
45 prepared from (13*E*)-(5*RS*,6*RS*,9 α ,11 α ,15*S*,17*S*)-5-iodo-6,9-epoxy-11,15-dihydroxy-17,20-dimethylprost-13-enoic acid methyl ester [prepared as described in Reference Example 2(b)].
TLC (developing solvent, ethyl acetate):
R_f = 0.70;

- IR (liquid film): ν = 2950, 2880, 1745 cm⁻¹;
50 NMR (CDCl₃ solution): δ = 5.5—5.12 (2H, m), 4.63—4.4 (2H, m), 3.54 (3H, s).

REFERENCE EXAMPLE 4

(13*E*)-(9 α ,11 α ,15*S*)-6-Oxo-9-hydroxy-11,15-bis-(tetrahydropyran-2-yloxy)prost-13-enoic acid methyl ester

- Under an atmosphere of nitrogen, a solution of 970 mg of (13*E*)-(5*RS*,6*RS*,9 α ,11 α ,15*S*)-5-bromo-6,9-epoxy-11,15-bis(tetrahydropyran-2-yloxy)prost-13-enoic acid methyl ester (prepared as described in Reference Example 1) and 2 ml of DBU was stirred at room temperature overnight, and then
55 cooled to 0°C. 6 ml of water was added to the reaction mixture, which was then acidified to pH 1 with 1N hydrochloric acid at 0°C, and extracted with ethyl acetate. The extract was washed with an aqueous solution of sodium bicarbonate and an aqueous solution of sodium chloride, dried over magnesium
60 sulphate and concentrated under reduced pressure to give the crude title compound having the following physical characteristic:—

TLC (developing solvent, ethyl acetate:n-hexane = 1:1);
R_f = 0.31.

REFERENCE EXAMPLE 5

(13E)-(9 α ,11 α ,15S,16S)-6-Oxo-9-hydroxy-11,15-bis-(tetrahydropyran-2-yloxy)-16-methylprost-13-enoic acid methyl ester

Under an atmosphere of nitrogen, a solution of 2.233 g of (13E)-(5RS,6RS,9 α ,11 α ,15S,16S)-5-bromo-6,9-epoxy-11,15-bis(tetrahydropyran-2-yloxy)-16-methylprost-13-enoic acid methyl ester [prepared as described in Reference Example 1(a)] and 7.4 ml of DBU was stirred at 70°C for 3 hours, and then cooled to 0°C. To the reaction mixture were added 37 ml of 1N hydrochloric acid and 37 ml of phosphate buffer solution (pH 6.68) with cooling to 0°C. The reaction mixture was extracted quickly with diethyl ether. The extract was dried over magnesium sulphate and concentrated under reduced pressure to give an oily product. To a solution of the oily product thus obtained in 40 ml of tetrahydrofuran were added dropwise 4 ml of water and 4 ml of 65% (v/v) aqueous acetic acid and the mixture was stirred at room temperature for 2 hours and then extracted with ethyl acetate. The extract was washed with water, an aqueous solution of sodium bicarbonate and an aqueous solution of sodium chloride, dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of cyclohexane and ethyl acetate (1:1) as eluent to give 1.323 g of the title compound having the following physical characteristics:—

TLC (developing solvent, cyclohexane:ethyl acetate = 1:1):

R_f = 0.34;

IR (liquid film): ν = 3425, 1740, 1710, 970 cm⁻¹;

20 NMR (CDCl₃ solution): δ = 5.7—5.3 (2H, m), 4.75—4.4 (2H, m), 3.66 (3H, s), 4.3—3.25 (7H, m), 1.05—0.7 (6H, m).

The following compound was prepared by the same procedure as described above.

25 (a) (13E)-(9 α ,11 α ,15S,17S)-6-Oxo-9-hydroxy-11,15-bis(tetrahydropyran-2-yloxy)-17,20-dimethylprost-13-enoic acid methyl ester, having the following physical characteristics, was prepared from (13E)-(5RS,6RS,9 α ,11 α ,15S,17S)-5-iodo-6,9-epoxy-11,15-bis(tetrahydropyran-2-yloxy)-17,20-dimethylprost-13-enoic acid methyl ester [prepared as described in Reference Example 3(a)].

TLC (developing solvent, cyclohexane:ethyl acetate = 1:1):

R_f = 0.33;

IR (liquid film): ν = 2950, 2880, 1745 cm⁻¹;

30 NMR (CDCl₃ solution): δ = 5.51—5.15 (2H, m), 4.66—4.36 (2H, m), 3.51 (3H, s).

EXAMPLE 1

(13E)-(11 α ,15S)-6,9-Dioxo-11,15-bis(tetrahydropyran-2-yloxy)prost-13-enoic acid methyl ester

To a solution of crude (13E)-(9 α ,11 α ,15S)-6-oxo-9-hydroxy-11,15-bis(tetrahydropyran-2-yloxy)prost-13-enoic acid methyl ester (prepared as described in Reference Example 4) in 10 ml of diethyl ether was added 10 ml of a chromic acid solution (obtained from 760 mg of chromium trioxide, 2.56 g of manganese sulphate, 0.84 ml of sulphuric acid and 19 ml of water) at 0° to 5°C, and the mixture was stirred at the same temperature for 1 hour. The reaction mixture was extracted with diethyl ether and the extract was washed with an aqueous solution of sodium bicarbonate and an aqueous solution of sodium chloride, dried over magnesium sulphate and concentrated under reduced pressure.

40 The residue was purified by column chromatography on silica gel using a mixture of n-hexane and ethyl acetate (17:3) as eluent to give 480 mg of the title compound having the following physical characteristic:—

TLC (developing solvent, ethyl acetate:n-hexane = 1:1):

R_f = 0.45.

45 The following compound was prepared by the same procedure as described above. (a) (13E)-(11 α ,15S,17S)-6,9-Dioxo-11,15-bis(tetrahydropyran-2-yloxy)-17,20-dimethylprost-13-enoic acid methyl ester, having the following physical characteristics, was prepared from (13E)-(9 α ,11 α ,15S,17S)-6-oxo-9-hydroxy-11,15-bis(tetrahydropyran-2-yloxy)-17,20-dimethylprost-13-enoic acid methyl ester [prepared as described in Reference Example 5 (a)].

50 TLC (developing solvent, cyclohexane:ethyl acetate = 2:1):

R_f = 0.39;

IR (liquid film): ν = 2950, 2880, 1750, 1720 cm⁻¹;

NMR (CDCl₃ solution): δ = 5.6—5.21 (2H, m), 4.66—4.45 (2H, m), 3.51 (3H, s).

EXAMPLE 2

55 (13E)-(11 α ,15S)-6,9-Dioxo-11,15-dihydroxyprost-13-enoic acid methyl ester (6-oxo-PGE₁ methyl ester)

To a solution of 480 mg of (13E)-(11 α ,15S)-6,9-dioxo-11,15-bis(tetrahydropyran-2-yloxy)prost-13-enoic acid methyl ester (prepared as described in Example 1) in 1 ml of tetrahydrofuran was added 3 ml of 65% (v/v) aqueous acetic acid and the mixture was stirred at 45°C for 3 hours. The reaction mixture was diluted with 16 ml of water and extracted with a mixture of ethyl acetate and n-hexane (1:1). The extract was washed with water, an aqueous solution of sodium bicarbonate and an aqueous solution of sodium chloride, dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of ethyl acetate and n-

hexane (1:1) as eluent to give 177 mg of the title compound having the following physical characteristics:—

TLC (developing solvent, ethyl acetate): $R_f = 0.32$;

IR (liquid film): $\nu = 3630\text{--}3510, 1740, 1723, 1440, 1372, 1242, 1178, 1160, 1078, 975\text{ cm}^{-1}$;

5 NMR (CDCl_3 solution): $\delta = 5.65\text{--}5.40$ (2H, m), 4.28—3.85 (2H, m), 3.65 (3H, s), 2.93—2.05 (10H, m), 1.00—0.75 (3H, m). 5

The following compound was prepared by the same procedure as described above.

10 (a) (13*E*)-(11 α ,15*S*,17*S*)-6,9-Dioxo-11,15-dihydroxyl-17,20-dimethylprost-13-enoic acid methyl ester [6-oxo-17*S*,20-dimethyl-PGE₁ methyl ester], having the following physical characteristics, was prepared from (13*E*)-(11 α ,15*S*,17*S*)-6,9-dioxo-11,15-bis(tetrahydropyran-2-yloxy)17,20-dimethylprost-13-enoic acid methyl ester [prepared as described in Example 1(a)]. 10

TLC (developing solvent, ethyl acetate): $R_f = 0.39$;

IR (liquid film): $\nu = 2980, 2950, 2890, 1750, 1720, 1440\text{ cm}^{-1}$;

NMR (CDCl_3 solution): $\delta = 5.65\text{--}5.50$ (2H, m), 4.3—3.9 (2H, m), 3.67 (3H, s), 1.0—0.7 (6H, m).

15 EXAMPLE 3

α -Cyclodextrin clathrate of 6-oxo-17*S*,20-dimethyl-PGE₁ methyl ester

20 A solution of 3.64 mg of 6-oxo-17*S*,20-dimethyl-PGE₁ methyl ester [prepared as described in Example 2(a)] in 0.6 ml of ethanol was added to a solution of 110.66 mg of α -cyclodextrin in 2 ml of water and the mixture was stirred at room temperature for 5 minutes. The mixture was concentrated under reduced pressure to give 98.22 mg of the α -cyclodextrin clathrate of the compound specified in the title. The content of 6-oxo-17*S*,20-dimethyl-PGE₁ methyl ester in the product was 3.2% by weight. 20

EXAMPLE 4

β -Cyclodextrin clathrate of 6-oxo-17*S*,20-dimethyl-PGE₁ methyl ester

25 A solution of 3.35 mg of 6-oxo-17*S*,20-dimethyl-PGE₁ methyl ester [prepared as described in Example 2(a)] in 0.6 ml of ethanol was added to a solution of 41.9 mg of β -cyclodextrin in 2.1 ml of water and the mixture was stirred at room temperature for 5 minutes. The mixture was concentrated under reduced pressure to give 35.28 mg of the β -cyclodextrin clathrate of the compound specified in the title. The content of 6-oxo-17*S*,20-dimethyl-PGE₁ methyl ester in the product was 8.1% by weight. 25

30 The present invention includes within its scope pharmaceutical compositions which comprise at least one new therapeutically useful compound of general formula IV or cyclodextrin clathrate thereof, or, when R^1 in formula IV represents a hydrogen atom non-toxic salt thereof, together with a pharmaceutical carrier or coating. In clinical practice the new compounds of general formula IV will normally be administered orally, rectally or parenterally. 30

35 Solid compositions for oral administration include compressed tablets, pills, dispersible powders, and granules. In such solid compositions one or more of the active compounds is, or are, admixed with at least one inert diluent such as calcium carbonate, potato starch, alginic acid, lactose or mannitol. The compositions may also comprise, as is normal practice, additional substances other than inert diluents, e.g. lubricating agents, such as magnesium stearate. Liquid compositions for oral administration include pharmaceutically-acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert 40 diluents commonly used in the art, such as water and liquid paraffin. Besides inert diluents such compositions may also comprise adjuvants, such as wetting and suspending agents, and sweetening, flavouring, perfuming and preserving agents. The compositions according to the invention, for oral administration, also includes capsules of absorbable material such as gelatin containing one or more of the active substances with or without the addition of diluents or excipients. 40

45 Solid compositions for rectal administration include suppositories formulated in manner known *per se* and containing one or more of the active compounds. 45

50 Preparations according to the invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or suspending media are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. These compositions may also include adjuvants such as preserving, wetting, emulsifying and dispersing agents. They may be sterilised, for example, by filtration through a bacteria-retaining filter, by incorporation of sterilising agents in the compositions or by irradiation. They may also be manufactured in the form of sterile solid compositions, which can be dissolved in sterile water or some other sterile injectable medium immediately before use. 50

55 The percentage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage for the therapeutic effect desired shall be obtained. Obviously several unit dosage forms may be administered at about the same time. In general, the preparations should normally contain at least 0.025% by weight of active substance when required for administration by injection; for oral administration the preparations will 60 normally contain at least 0.1% by weight of active substance. The dose employed depends upon the desired therapeutic effect, the route of administration and the duration of the treatment. 60

In the human adult, the doses per person are generally between 0.005 and 5 mg. by oral administration in the treatment of hypertension; between 0.005 and 5 mg. by oral administration in the

treatment of disorders of the peripheral circulation, between 0.01 and 50 mg by oral administration in the prevention and treatment of cerebral thrombosis and myocardial infarction and between 0.0005 and 1 mg. by oral administration in the treatment of gastric ulceration.

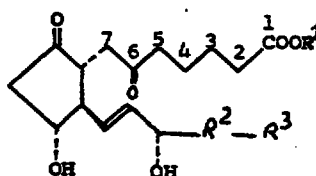
The following Example illustrates pharmaceutical compositions according to the invention.

5 EXAMPLE 5

6-Oxo-17S,20-dimethyl-PGE₁ methyl ester (2 mg) was dissolved in ethanol (10 ml), mixed with mannitol (18.5 g), sieved through a 30-mesh sieve, dried at 30°C for 90 minutes and again sieved through a 30-mesh sieve. Aerosil (microfine silica, 200 mg) was added and the powder obtained was machine filled into one hundred No. 2 hard gelatin capsules to give capsules each containing 20 μ g of 6-oxo-17S,20-dimethyl-PGE₁ methyl ester, which after swallowing of the capsule is released into the stomach. "Aerosil" is a registered Trade Mark.

CLAIMS

1. 6-Oxo-17,20-dimethyl-prostaglandin E₁ analogues of the general formula:



IV

15 (wherein R¹ represents a hydrogen atom or a straight- or branched-chain alkyl group containing from 1 to 4 carbon atoms, the grouping —R²—R³ represents a 2-methylhexyl group, and the dotted line attached to the C—11 and C—15 carbon atoms represents α -configuration) and cyclodextrin clathrates of such acids and esters and, when R¹ represents a hydrogen atom, non-toxic salts thereof.

2. Prostaglandin analogues according to claim 1 wherein R¹ represents a hydrogen atom or a methyl group.

3. (13E)-(11 α ,15S,17S)-6,9-Dioxo-11,15-dihydroxy-17,20-dimethylprost-13-enoic acid methyl ester.

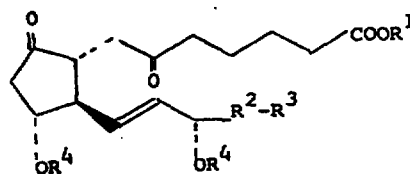
4. Non-toxic salts of the prostaglandin analogues as claimed in claim 1 wherein R¹ represents a hydrogen atom and the other symbols are as defined in claim 1.

5. Cyclodextrin clathrates of a prostaglandin analogue as claimed in claim 1, 2 or 3.

6. α -Cyclodextrin clathrate of the prostaglandin analogue claimed in claim 3.

7. β -Cyclodextrin clathrate of the prostaglandin analogue claimed in claim 3.

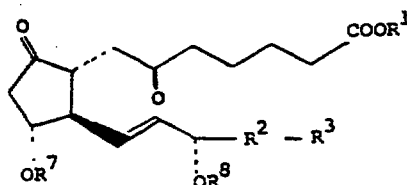
8. Process for the preparation of prostaglandin analogues of the general formula depicted in claim 1, wherein the various symbols are as defined in claim 1, which comprises the hydrolysis to hydroxy groups of the groups OR⁴ of a compound of the general formula:—



V

wherein R⁴ represents a tetrahydropyran-2-yl or tetrahydrofuran-2-yl group, each such group being unsubstituted or substituted by at least one alkyl group, or represents a 1-ethoxyethyl group, and the other symbols are as defined in claim 1.

9. Process for the preparation of prostaglandin analogues of the general formula depicted in claim 1 wherein the various symbols are as defined in claim 1, which comprises the hydrolysis to hydroxy groups of the groups —OR⁷ and —OR⁸ of a compound of the general formula:—



XII

wherein R⁷ and R⁸, which may be the same or different, each represents a tetrahydropyran-2-yl or tetrahydrofuran-2-yl group, each such group being unsubstituted or substituted by at least one alkyl

treatment of disorders of the peripheral circulation, between 0.01 and 50 mg by oral administration in the prevention and treatment of cerebral thrombosis and myocardial infarction and between 0.0005 and 1 mg. by oral administration in the treatment of gastric ulceration.

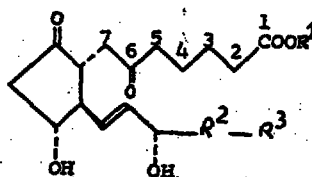
The following Example illustrates pharmaceutical compositions according to the invention.

5 EXAMPLE 5

6-Oxo-17S,20-dimethyl-PGE₁ methyl ester (2 mg) was dissolved in ethanol (10 ml), mixed with mannitol (18.5 g), sieved through a 30-mesh sieve, dried at 30°C for 90 minutes and again sieved through a 30-mesh sieve. Aerosil (microfine silica, 200 mg) was added and the powder obtained was machine filled into one hundred No. 2 hard gelatin capsules to give capsules each containing 20 µg of 6-oxo-17S,20-dimethyl-PGE₁ methyl ester, which after swallowing of the capsule is released into the stomach. "Aerosil" is a registered Trade Mark.

CLAIMS

1. 6-Oxo-17,20-dimethyl-prostaglandin E₁ analogues of the general formula:



IV

15 (wherein R¹ represents a hydrogen atom or a straight- or branched-chain alkyl group containing from 1 15
to 4 carbon atoms, the grouping —R²—R³ represents a 2-methylhexyl group, and the dotted line
attached to the C—11 and C—15 carbon atoms represents α -configuration) and cyclodextrin clathrates
of such acids and esters and, when R¹ represents a hydrogen atom, non-toxic salts thereof.

2. Prostaglandin analogues according to claim 1 wherein R¹ represents a hydrogen atom or a methyl group.

3. (13*E*)-(11 α ,15*S*,17*S*)-6,9-Dioxo-11,15-dihydroxy-17,20-dimethylprost-13-enoic acid methyl ester.

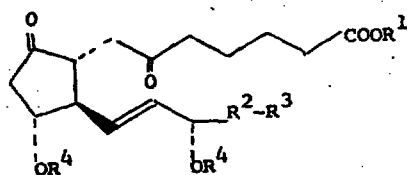
4. Non-toxic salts of the prostaglandin analogues as claimed in claim 1 wherein R¹ represents a hydrogen atom and the other symbols are as defined in claim 1.

25 5. Cyclodextrin clathrates of a prostaglandin analogue as claimed in claim 1, 2 or 3.

6. α -Cyclodextrin clathrate of the prostaglandin analogue claimed in claim 3.

7. β -Cyclodextrin clathrate of the prostaglandin analogue claimed in claim 3.

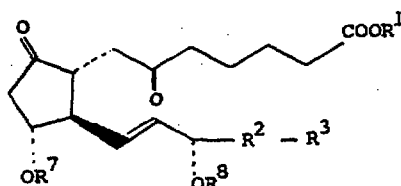
8. Process for the preparation of prostaglandin analogues of the general formula depicted in claim 1, wherein the various symbols are as defined in claim 1, which comprises the hydrolysis to hydroxy groups of the groups OR⁴ of a compound of the general formula:—



V

wherein R⁴ represents a tetrahydropyran-2-yl or tetrahydrofuran-2-yl group, each such group being unsubstituted or substituted by at least one alkyl group, or represents a 1-ethoxyethyl group, and the other symbols are as defined in claim 1.

35 9. Process for the preparation of prostaglandin analogues of the general formula depicted in claim 1 wherein the various symbols are as defined in claim 1, which comprises the hydrolysis to hydroxy groups of the groups —OR⁷ and —OR⁸ of a compound of the general formula:— 35



XII

wherein R⁷ and R⁸, which may be the same or different, each represents a tetrahydropyran-2-yl or tetrahydrofuran-2-yl group, each such group being unsubstituted or substituted by at least one alkyl



group, a 1-ethoxyethyl group, or a trimethylsilyl group, with the proviso that at least one of the symbols R^7 and R^8 represents a trimethylsilyl group, and the other symbols are as defined in claim 1.

10. Process according to claim 8 wherein the symbol R^4 represents the tetrahydropyran-2-yl group.

5 11. Process according to claim 9, wherein one of the symbols R^7 and R^8 represents the tetrahydrofuran-2-yl group and the other represents the trimethylsilyl group. 5

12. Process according to any one of claims 8 to 11 in which the hydrolysis of the OR^4 group, or the OR^7 and OR^8 groups, to hydroxy groups is carried out by mild acidic hydrolysis with an aqueous solution of an organic acid, or an aqueous solution of an inorganic acid at a temperature from ambient to 75°C or with an anhydrous solution of an organic acid in a lower alkanol at a temperature of from 10° to 45°C . 10 10

13. Process according to any one of claims 8 to 12 in which the hydrolysis is carried out using an aqueous solution of an organic acid or an aqueous solution of an inorganic acid, in the presence of an inert organic solvent miscible with water and at a temperature from ambient to 45°C . 15

14. Process according to any one of claims 8 to 13 in which the hydrolysis is carried out with a mixture of hydrochloric acid, water and tetrahydrofuran, a mixture of hydrochloric acid, water and methanol, a mixture of acetic acid, water and tetrahydrofuran, or a mixture of *p*-toluenesulphonic acid and methanol. 15

15. Process according to any one of claims 8 to 14 followed by the step of converting by methods known *per se* a prostaglandin analogue of general formula IV depicted in claim 1, wherein R^1 represents a hydrogen atom and the other symbols are as defined in claim 1, into a corresponding ester of that formula wherein R^1 is other than a hydrogen atom. 20 20

16. Process according to any one of claims 8 to 15 followed by the step of converting by methods known *per se* a prostaglandin analogue of general formula IV depicted in claim 1, wherein the various symbols are as defined in claim 1, into a cyclodextrin clathrate. 25 25

17. Process according to any one of claims 8 to 14 followed by the step of converting by methods known *per se* a prostaglandin analogue of general formula IV depicted in claim 1, wherein R^1 represents a hydrogen atom and the other symbols are as defined in claim 1, into a non-toxic salt thereof. 30

18. Process for the preparation of prostaglandin analogues of general formula IV depicted in claim 1, wherein the various symbols are as defined in claim 1, substantially as described in Example 2. 30 30

19. Prostaglandin analogues of general formula IV depicted in claim 1, and cyclodextrin clathrates and, when R^1 in general formula IV depicted in claim 1 represents a hydrogen atom, non-toxic salts thereof, when prepared by the process claimed in any one of claims 8 to 18. 35

20. Pharmaceutical compositions which comprise as active ingredient, at least one prostaglandin analogue as claimed in any one of claims 1 to 7 and 19 or a cyclodextrin clathrate thereof or, when R^1 in general formula IV depicted in claim 1 represents a hydrogen atom, a non-toxic salt thereof, in association with a pharmaceutical carrier or coating. 35 35

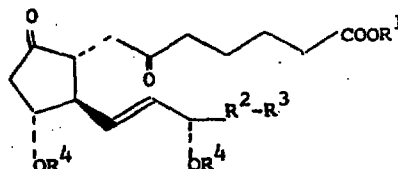
21. Pharmaceutical compositions according to claim 20 which comprise, as active ingredient, the prostaglandin compound claimed in claim 3, or a cyclodextrin clathrate thereof. 40

22. Pharmaceutical compositions according to claim 20 or 21 substantially as hereinbefore described. 40 40

23. Pharmaceutical compositions according to claim 20 or 21 substantially as hereinbefore described in Example 5.

24. A compound as claimed in any one of claims 1 to 7 and 19 for use in a method for the treatment of hypertension, the treatment of disorders of the peripheral circulation, in the prevention and treatment of cerebral thrombosis and myocardial infarction and in the treatment of gastric ulceration. 45 45

25. Compounds of the general formula:

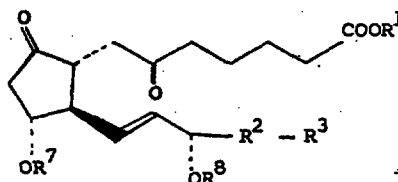


V

wherein R^4 is as defined in claim 8 and the other symbols are as defined in claim 1.

50 26. Compounds of the general formula:—

50



XII

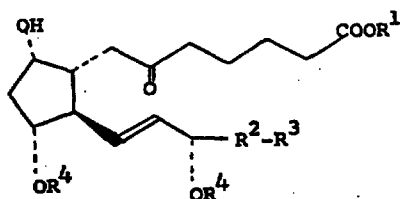


* C L M S *

(2)

wherein R^7 and R^8 are as defined in claim 9 and the other symbols are as defined in claim 1.

27. Compounds of the general formula:



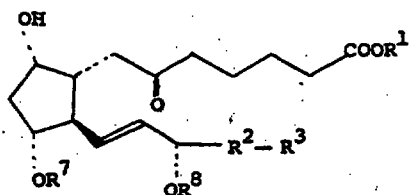
VI

wherein R^4 is as defined in claim 8 and the other symbols are as defined in claim 1.

5

28. Compounds of the general formula:

5



XIII

wherein R^7 and R^8 are as defined in claim 9, and the other symbols are as defined in claim 1.