

PATENT SPECIFICATION

(11) 1 540 427

- (21) Application No. 15982/76 (22) Filed 20 April 1976
 (61) Patent of Addition to No. 1416410 dated 28 Dec. 1973
 (31) Convention Application No. 646316
 (32) Filed 5 Jan. 1976 in
 (33) United States of America (US)
 (44) Complete Specification published 14 Feb. 1979
 (51) INT CL² C07C 177/00 A61K 31/19 31/215 C08B 37/16//C07D 307/93 309/12 C07F 7/08 9/40 11/00
 (52) Index at acceptance

C2C 1175 147X 1672 200 213 215 220 225 227 22Y 247 248 253
 257 259 25Y 275 28X 294 295 302 304 30Y 350 351 352
 353 355 35Y 360 361 362 364 366 367 368 36Y 387 388
 389 38X 38Y 401 409 40Y 43X 46Y 47X 490 491 500 502
 509 50Y 623 624 625 628 633 634 635 638 652 655 658
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 TA TU UF UL WD
 C2P 3B11A 3B14A 3B19E 7
 C3U 2CX 4L

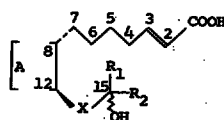


(54) PROSTAGLANDIN ANALOGUES

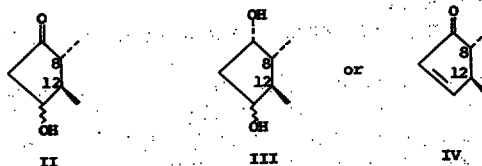
(71) We, ONO PHARMACEUTICAL CO. LTD., a Japanese Body Corporate of 14 Doshomachi 2-Chome, Higashi-ku, Osaka 541, Japan, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new prostaglandin analogues. It is an improvement in or modification of the invention described and claimed in the Specification of our Application No. 60040/73 (Serial No. 1,416,410).

In the Specification of our Application No. 60040/73 (Serial No. 1,416,410) we have described and claimed *inter alia trans-Δ²*-prostaglandin analogues of the general formula:—



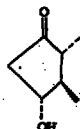
(wherein A represents a grouping of the formula:



X represents ethylene (i.e. —CH₂CH₂—) or *trans*-vinylene (i.e. —CH=CH—), R₁ represents a straight- or branched-chain alkyl radical containing from 1 to 10 carbon atoms or a straight- or branched-chain alkyl radical containing from 1 to 6 carbon atoms carrying a phenyl substituent or a cycloalkyl substituent of 5 to 7 carbon atoms, R₂ represents a hydrogen atom or a straight- or branched-chain alkyl radical containing from 1 to 4 carbon atoms, the wavy line indicates attachment of the hydroxy radical to the carbon atom in alpha or beta configuration and the C₂—C₃ double bond is *trans*) and alkyl esters thereof having 1 to 10 carbon atoms in a straight- or branched-chain, and cyclodextrin clathrates of such acids or esters, and non-toxic salts of such acids, with the exclusion of *trans*-2,3-didehydro-PGE₁. In the aforesaid Specification it is disclosed that the compounds possess the known valuable pharmacological properties typical of prostaglandins in a selective fashion including, in particular, hypotensive activity, inhibitory activity on blood platelet aggregation, inhibitory activity on gastric acid secretion, and gastric ulceration, and

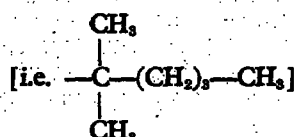
bronchodilator activity and are useful in the treatment of hypertension, in the treatment of disorders of the peripheral circulation, in the prevention and treatment of cerebral thrombosis and myocardial infarction, in the treatment of gastric ulceration and in the treatment of asthma.

It has now been found after further research and experimentation that *trans*- Δ^2 -prostaglandin analogues of general formula I wherein A represents the grouping of the formula:

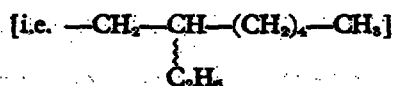


V

X represents *trans*-vinylene, R_1 represents the 1,1-dimethylpentyl group

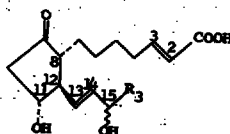


or the 2(ξ)-ethylheptyl group



and R_2 represents a hydrogen atom [viz. 16,16-dimethyl-*trans*-2,3-didehydro-PGE₁, and 17(ξ),20-diethyl-*trans*-2,3-didehydro-PGE₁] and methyl esters thereof, the cyclodextrin clathrates of such acids and esters, and non-toxic salts of the acids, possess unexpectedly outstanding pharmacological properties.

The present invention is concerned with all such compounds in the 'natural' analogues of the general formula:



VI

(wherein R_3 represents the 1,1-dimethylpentyl or 2(ξ)-ethylheptyl group, the wavy line indicates attachment of the hydroxy group in beta or, preferably, alpha configuration and the C_2-C_3 and $\text{C}_{13}-\text{C}_{14}$ double bonds are *trans*) and methyl esters thereof, and cyclodextrin clathrates of such acids or esters, and non-toxic (e.g. sodium) salts of such acids.

The present invention is concerned with all such compounds in the 'natural' form as depicted.

As will be apparent to those skilled in the art, the compounds depicted in general formula VI have four centres of chirality, these four centres of chirality being at the alicyclic ring carbon atoms identified as 8, 11 and 12 and at the C-15 carbon atom which has attached to it a hydroxy group. A further centre of chirality occurs when the symbol R_3 represents a 2(ξ)-ethylheptyl group. The presence of chirality leads, as is well known, to the existence of isomerism. All isomers of general formula VI and mixtures thereof are to be considered within the scope of general formula VI.

The prostaglandin analogue of formula VI wherein R_3 represents the 1,1-dimethyl pentyl group, and the methyl ester, and non toxic salts thereof, have been found to possess exceptionally good abortifacient activity and stimulatory activity on uterine contraction, activities not mentioned in the Specification of Application No. 60040/73 (Serial No. 1,416,410) in respect of any specific compound conforming to general formula I disclosed therein, and are accordingly useful in the termination of pregnancy and induction of labour in pregnant female mammals and in the control of oestrus, contraception and menstrual regulation in female mammals. Such compounds also have hypotensive activity.

The prostaglandin analogue of formula VI wherein R_3 represents the 2(ξ)-ethyl-

heptyl group, and the methyl ester and non-toxic salts thereof, have been found to possess an exceptionally good hypotensive activity and are accordingly useful in the treatment of hypertension and in the treatment of disorders of the peripheral circulation.

The prostaglandin compounds of the present invention have relatively low potencies in inducing diarrhoea in comparison with their potencies in respect of the valuable pharmacological properties hereinbefore mentioned, and may accordingly be used for the stated purposes at appropriate rates of administration which do not induce diarrhoea as an undesired side effect.

The preferred compound of the invention in respect of its abortifacient activity and stimulatory activity on uterine contraction is 16,16-dimethyl-*trans*-2,3-didehydro-PGE₁ methyl ester, and the preferred compound of the invention in respect of its hypotensive activity is 17(ξ),20-diethyl-*trans*-2,3-didehydro-PGE₁ methyl ester.

For example, in standard laboratory tests, on oral administration to the conscious spontaneously hypertensive rat, 17(ξ),20-diethyl-*trans*-2,3-didehydro-PGE₁ methyl ester produces falls in blood pressure of 15 mm.Hg, 10 mm.Hg, and 14 mm.Hg, at 0.5, 1 and 3 hours after administration, respectively, at a dose of 0.1 mg./kg. animal body weight, 33 mm.Hg, 19 mm.Hg, 13 mm.Hg, and 11 mm.Hg, at 0.5, 1, 3 and 5 hours after administration, respectively, at a dose of 0.3 mg./kg. animal body weight, and 44 mm.Hg, 39 mm.Hg, 21 mm.Hg, and 20 mm.Hg, at 0.5, 1, 3 and 5 hours after administration, respectively, at a dose of 1.0 mg./kg. animal body weight.

In the above experiments soft faeces were observed only in one out of six rats at the dose of 0.3 mg./kg. animal body weight and in none of six rats at the doses of 0.1 mg./kg. animal body weight and 1.0 mg./kg. animal body weight, respectively. These results indicate that 17(ξ),20-diethyl-*trans*-2,3-didehydro-PGE₁ methyl ester has a strong hypotensive activity and a very weak diarrhoea-producing (side effect) activity.

16,16-Dimethyl-*trans*-2,3-didehydro-PGE₁ methyl ester (i) stimulates uterine contraction when administered intravenously to the pregnant rat on the 20th day of gestation at a dose of 0.5 μg./kg. animal body weight, (ii) produces a fall of the blood pressure when administered intravenously to the allobarbital-anaesthetised dog at a dose of 1 μg./kg. animal body weight, and (iii) produces diarrhoea at a dose of 1,200 μg./kg. animal body weight by oral administration in 50% of mice so treated.

Of the pharmacological activities of 16,16-dimethyl-*trans*-2,3-didehydro-PGE₁ methyl ester, (i) uterine contractile activity is the useful effect and (ii) hypotensive and (iii) diarrhoea-producing activities are considered to be undesired effects. The pharmacological activities on rats of 16,16-dimethyl-*trans*-2,3-didehydro-PGE₁ methyl ester and of prostaglandin analogues already disclosed in the Specification of our Application No. 60040/73 (Serial No. 1,416,410), e.g. 16(R)-methyl-*trans*-2,3-didehydro-PGE₁, 16(ξ)-phenyl-18,19,20-trinor-*trans*-2,3-didehydro-PGE₁ and 15(ξ)-methyl-*trans*-2,3-didehydro-PGE₁, are compared in the following Table.

(16)

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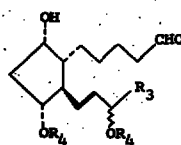
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TABLE

	(i) Uterine contraction activity $\mu\text{g./kg.}$	(ii) Hypotensive activity $\mu\text{g./kg.}$	(iii) Production of diarrhoea activity $\mu\text{g./kg.}$	(ii)/(i)	(iii)/(i)
16(R)-methyl- <i>trans</i> - 2,3-didihydro-PGE ₁	5	0.05	85	$0.05/5$ $= 0.01$	$85/5 = 17$
16(S)-phenyl-18,19,20- trien- <i>trans</i> -2,3-didihydro- PGE ₁	20	0.02	1940	$0.02/20$ $= 0.001$	$1940/20$ $= 97$
15(S)-methyl- <i>trans</i> - 2,3-didihydro-PGE ₁	5	1	20	$1/5 = 0.2$	$20/5 = 4$
16,16-dimethyl- <i>trans</i> - 2,3-didihydro-PGE ₁ methyl ester	0.5	1	1200	$1/0.5 = 2$	$1200/0.5$ $= 2400$

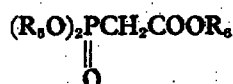
As is to be noted from the Table, 16,16-dimethyl-*trans*-2,3-didehydro-PGE₁ methyl ester produces a strong desired effect (uterine contraction) which is at least 10 times more potent than the other compounds. Moreover, the selectivity index (separation of desired activity from side-effects, i.e. the (ii)/(i) or (iii)/(i) ratio) of 16,16-dimethyl-*trans*-2,3-didehydro-PGE₁ methyl ester is very much higher than those of the known compounds. These data indicate that 16,16-dimethyl-*trans*-2,3-didehydro-PGE₁ methyl ester has a strong uterine contraction activity far superior to the other compounds tested and is better and safer in use in the termination of pregnancy and induction of labour in pregnant female mammals and in the control of oestrus, contraception and menstrual regulation in female mammals, than the other compounds tested.

According to the feature of the present invention, the *trans*- Δ^2 -prostaglandins of general formula VI and their methyl esters are prepared by the process which comprises reacting a cyclopentane derivative of the general formula:



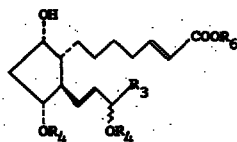
VII

(wherein R₄ represents a 2-tetrahydropyranyl group unsubstituted or substituted by at least one alkyl radical or a 1-ethoxyethyl group, R₄ preferably being the 2-tetrahydropyranyl group, R₃ is as hereinbefore defined and the wavy line indicates attachment of the OR₄ group to the carbon atom in alpha or beta configuration) with a dialkyl phosphonate of the general formula:



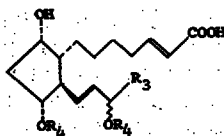
VIII

(wherein R₅ represents a methyl or ethyl radical, and R₆ represents the methyl radical or a straight- or branched-chain alkyl radical containing from 2 to 12 carbon atoms), optionally hydrolysing when R₆ is the methyl radical, or hydrolysing when R₆ is an alkyl radical containing from 2 to 12 carbon atoms, the resulting *trans*- Δ^2 -prostaglandin ester of the general formula:



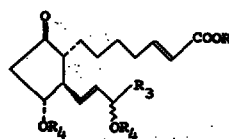
IX

(wherein R₃, R₄, R₆ and the wavy line have the meanings hereinbefore specified) to the corresponding acid of the general formula:



X

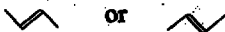
(wherein R₃, R₄ and the wavy line have the meanings hereinbefore specified), converting by methods known *per se* the 9 α -hydroxy group in the compound of general formula IX (wherein R₆ represents the methyl radical) or X to an oxo group, and hydrolysing the OR₄ groups in the resulting *trans*- Δ^2 -prostaglandin compound of the general formula:



XI

(wherein R represents a hydrogen atom or the methyl radical, and R₃, R₄ and the wavy line have the meanings hereinbefore specified)

have the meanings hereinbefore specified) to hydroxy groups to obtain a PGE compound of general formula VI or a methyl ester thereof. In general formulae VII, IX, X and XI the double bonds depicted are *trans* as are all other double bonds depicted



in following formulae; *cis* double bonds in following formulae are depicted



By the term "methods known *per se*" as used in this Specification is meant methods heretofore used or described in the chemical literature.

The reaction between the cyclopentane derivatives of general formula VII and the dialkyl phosphonates of general formula VIII (in the form of a sodio derivative formed, for example, by reaction of sodium hydride with the dialkyl phosphonate in an inert organic medium) is carried out under the normal conditions utilised for effecting a Wittig reaction, e.g. in an inert organic solvent at a temperature not exceeding 30°C. The reaction is preferably carried out by suspending a strong base, such as sodium hydride, in an inert organic medium (e.g. tetrahydrofuran or 1,2-dimethoxyethane), adding the dialkyl phosphonate thereby to form its sodio derivative with evolution of hydrogen, and adding to the resulting solution of the sodium dialkylphosphonate the cyclopentane derivative of general formula VII. By the Wittig reaction a *trans*- Δ^2 double bond is formed stereospecifically and a compound of general formula IX is obtained.

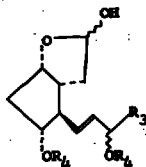
The hydrolysis of the alkyl esters of general formula IX to the corresponding acids of general formula X may be carried out according to methods known *per se*, for example by treatment of the ester with an aqueous solution of an alkali metal, e.g. sodium or potassium, hydroxide or carbonate in the presence of a water-miscible organic solvent, e.g. tetrahydrofuran or an alkanol containing from 1 to 4 carbon atoms, e.g. methanol.

The PGF alicyclic ring in the compounds of general formulae IX (wherein R_1 represents the methyl radical) and X can be converted into a PGE ring by methods known *per se* for the conversion of a hydroxy group in the 9-position of a prostaglandin to an oxo group, for example by means of a chromic acid solution (e.g. obtained from chromium trioxide, manganese sulphate and sulphuric acid in water) or Jones' reagent.

The OR_4 groups of the compounds of general formula XI may be converted to hydroxy groups by mild hydrolysis with an aqueous solution of an organic acid, e.g. acetic acid, or with a dilute aqueous inorganic acid, e.g. hydrochloric acid, advantageously in the presence of an organic solvent miscible with water, e.g. tetrahydrofuran or an alkanol containing from 1 to 4 carbon atoms, e.g. methanol. The mild hydrolysis may be carried out at a temperature ranging from ambient to 60°C. (preferably at a temperature below 45°C.) with an acid mixture, e.g. a mixture of hydrochloric acid with tetrahydrofuran or methanol, or a mixture of acetic acid, water and tetrahydrofuran.

The products of general formula VI or the methyl esters thereof may be purified by column chromatography on silica gel, which procedure may, when the intermediate compound of general formula XI is a mixture of compounds with the OR_4 group in the 15-position in α - and β -configurations, lead to a separation of the resulting 15 α -hydroxy and 15 β -hydroxy isomers of general formula VI or ester thereof.

The cyclopentane derivatives of general formula VII employed as starting materials in the aforedescribed process can be prepared from bicyclo-octane derivatives of the general formula:

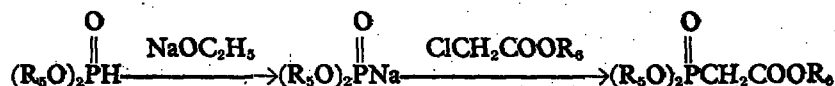


XII

(wherein R_3 , R_4 and have the meanings hereinbefore specified and the depicted double bond is *trans*) by application of procedures described in the Specification of

Application No. 60040/73 (Serial No. 1,416,410) for the preparation of analogous cyclopentane derivatives.

The dialkyl phosphonate starting materials of general formula VIII can be synthesised by the procedure described by G. M. Kosolapoff, *J. Amer. Chem. Soc.* 68, 1103 (1946), according to the reaction sequence:—



wherein R_5 and R_6 are as hereinbefore defined.

The compounds of general formula XII can be prepared using initially 2-oxa-6-syn-formyl-7-anti-acetoxy-cis-bicyclo[3,3,0]octan-3-one [E. J. Corey *et al.*, *J. Amer. Chem. Soc.*, 91, 5675 (1969)] and the sodio derivative of a dialkyl phosphonate of the general formula:



(wherein R_7 represents an alkyl group containing from 1 to 4 carbon atoms and R_8 is as hereinbefore defined) and applying thereto known procedures [see, for example, *J. Amer. Chem. Soc.*, 92, 397 (1970) and French Patent No. 7,215,314 (publication No. 2,134,673)].

The dialkyl phosphonates of general formula XIII can be prepared by reacting a solution of *n*-butyllithium in diethyl ether with a solution of a dialkyl methylphosphonate of the general formula:

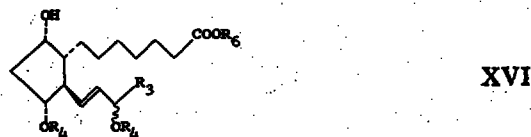


(wherein R_7 is as hereinbefore defined), e.g. dimethyl methyl phosphonate or diethyl methylphosphonate in tetrahydrofuran at a temperature below -50°C ., and then adding dropwise to the reaction mixture a solution of a compound of the general formula:



(wherein R_9 represents an alkyl group containing from 1 to 4 carbon atoms and R_{10} is as hereinbefore defined) in tetrahydrofuran at a temperature below -50°C ., for 2 to 4 hours, and then stirring for 2 to 18 hours at a temperature ranging from ambient to 0°C ., to give the desired dialkyl phosphonate of general formula XIII.

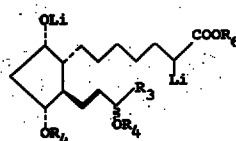
According to a further feature of the present invention the *trans*- Δ^2 -prostaglandin analogues of general formula VI, and their methyl esters, are prepared by the process which comprises reacting a compound of the general formula:—



(wherein the various symbols and $\sim$ are as hereinbefore defined, R_4 preferably being the 2-tetrahydropyranyl group) with a compound of the general formula:—

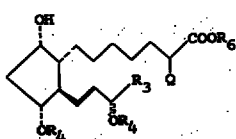


(wherein R_9 and R_{10} , which may be the same or different, each represents a straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms or a cycloalkyl group containing from 3 to 6 carbon atoms), e.g. lithium diisopropylamide, to obtain a lithium ester/enolate of the general formula:—



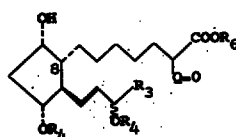
XVIII

(wherein the various symbols and $\sim$ are as hereinbefore defined), reacting the lithium ester enolate with benzene-selenenyl bromide (i.e. ϕSeBr in which ϕ represents the phenyl radical) or diphenyl diselenide or a dialkyl or diphenyldisulphide of the formula $\text{R}_{11}\text{SSR}_{11}$, wherein the symbols R_{11} both represent alkyl groups containing from 1 to 4 carbon atoms or phenyl radicals, hydrolysing the resulting intermediate to convert the $-\text{OLi}$ group attached to the cyclopentane ring to an α -hydroxy group and to obtain a compound of the general formula: —



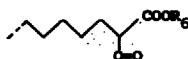
XIX

(wherein the various symbols and $\sim$ are as hereinbefore defined and Q represents $-\text{Se}\phi$, in which ϕ is as hereinbefore defined, or a group $-\text{SR}_{11}$, in which R_{11} is as hereinbefore defined), treating the resulting compound with hydrogen peroxide or sodium periodate, and decomposing the resulting compound of the general formula: —



XX

(wherein the various symbols and $\sim$ are as hereinbefore defined) to convert the grouping



attached to the 8-position of the cyclopentane ring to a *trans*- Δ^2 -grouping



wherein R_6 is as hereinbefore defined, i.e. to obtain a compound of general formula IX, wherein the various symbols and $\sim$ are as hereinbefore defined, and treating the compound of formula IX as hereinbefore described to obtain a prostaglandin analogue of general formula VI or methyl ester thereof.

The reaction between the prostaglandin compound of general formula XVI and the lithiated amine of general formula XVII is carried out in an organic solvent, for example by adding dropwise a solution of a prostaglandin compound of formula XVI in tetrahydrofuran to a solution of an amine of formula XVII in tetrahydrofuran at a low temperature, e.g. -70°C ., the ratio of the molecular equivalents of the compounds of formula XVI to XVII in the reaction mixture being 1:2 to 3. After completion of the addition of the prostaglandin solution, the reaction mixture is stirred at the same temperature for about 30 minutes to obtain a solution of the lithium ester enolate of formula XVIII.

The reaction between the lithium ester enolate of formula XVIII and benzene-selenenyl bromide, diphenyl diselenide or dialkyl or diphenyl disulphide is preferably carried out in tetrahydrofuran, diethyl ether, hexane or pentane or a mixture of two or more of them, tetrahydrofuran being the preferred solvent, at a low temperature, e.g. -70°C . Thus, to the lithium ester enolate solution obtained as described above there is added a solution in tetrahydrofuran of 3 or 4 molecular equivalents of benzeneselenenyl bromide or diphenyl diselenide, or 2 to 3 molecular equivalents of dialkyl or diphenyl disulphide, for each molecular equivalent of lithium ester enolate present, the temperature of the two solutions being -70°C . The reaction mixture is stirred at -70°C . (a) for one hour when a selenium compound is the

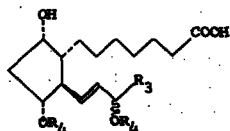
reactant or (b) for 30 minutes when a disulphide is the reactant, and subsequently at ambient temperature, e.g. 15°C. for 30 minutes. After addition of, for example, a small amount of a saturated aqueous ammonium chloride solution to the solution of the resulting prostaglandin intermediate to hydrolyze the —OLi group attached to the cyclopentane ring to an α -hydroxy group, the product of formula XIX is extracted with ethyl acetate.

When the product of formula XIX is a compound wherein Q is benzeneselenenyl, i.e. —Se ϕ , the ethyl acetate solution of the product is then treated with 5 to 7 molecular equivalents of hydrogen peroxide at a temperature below 30°C. or with 5 molecular equivalents of sodium periodate in the presence of a lower alkanol, preferably methanol and water, at a temperature below 20°C., preferably for about 24 hours, to form a compound of formula XX wherein O=Q— is benzeneselenenyl, i.e. —Se(O) ϕ , and stirring of the reaction mixture at a temperature of 25° to 30°C. for one hour results in decomposition of the compound to a compound of general formula IX, which can be separated from the reaction medium by methods known *per se* and purified by column chromatography in silica gel.

When the product of formula XIX is a compound wherein Q is a group —SR₁₁, R₁₁ being as hereinbefore defined, the product is separated from the ethyl acetate solution by methods known *per se* and treated with hydrogen peroxide or sodium periodate in the same way as hereinbefore described for a product of formula XIX wherein Q is benzeneselenenyl to obtain a compound of general formula XX wherein Q is a group —SR₁₁, R₁₁ being as hereinbefore defined, which can be separated from the reaction medium by methods known *per se*.

When the compound of formula XX is one wherein Q represents an alkylthio group —SR₁₂, wherein R₁₂ represents an alkyl group containing from 1 to 4 carbon atoms, the compound is dissolved in toluene and the solution stirred, preferably in the presence of a small amount of calcium carbonate, at a temperature of 100° to 120°C. for a period ranging from 5 to 24 hours to decompose the compound to a compound of general formula IX. When the compound of general formula XX is one wherein Q represents the phenylthio group, the compound is dissolved in carbon tetrachloride and the solution stirred, preferably in the presence of a small amount of calcium carbonate, at a temperature of about 50°C. for a period ranging from 5 to 24 hours to decompose the compound to a compound of general formula IX. The compounds of general formula IX can be separated from the reaction medium by methods known *per se* and purified by column chromatography on silica gel.

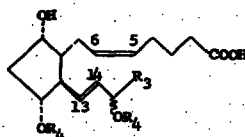
The starting materials of general formula XVI employed in this feature of the present invention can be prepared from the corresponding acids of the general formula:—



XXI

(wherein R₃, R₄ and $\sim$ are as hereinbefore defined) by reaction with (i) diazoalkane compounds, e.g. diazomethane, (ii) alcohols in the presence of dicyclohexylcarbodiimide as condensing agent, or (iii) alcohols 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. 1,362,956 and 1,364,125).

Compounds of general formula XXI may be prepared by reacting a bicyclo-octane derivative of general formula XII, wherein R₃, R₄ and $\sim$ are as hereinbefore defined, with (4-carboxybutylidene)triphenylphosphorane of the formula $\phi_3P=CH-(CH_2)_3-COOH$ (wherein ϕ is as hereinbefore defined) to obtain a cyclopentane derivative of the general formula:—



XXII

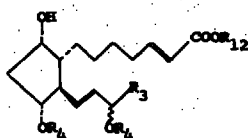
(wherein R₃, R₄ and $\sim$ are as hereinbefore defined) and hydrogenating by methods known *per se* the *cis*-double bond in the C₃—C₄ position to obtain an acid of general formula XXI. Mild reducing conditions should be used for the said reduc-

tion step in order to reduce only the C_5-C_6 double bond and not to affect the $C_{13}-C_{14}$ double bond. Suitably the reduction may be effected by hydrogenation in the presence of a hydrogenation catalyst, for example palladium on charcoal, in the presence of an inert organic solvent, for example a lower alkanol, e.g. methanol or ethanol, at laboratory temperature at normal or elevated pressure, e.g. at a hydrogen pressure from atmospheric to 15 kilograms per square centimetre. Advantageously the quantity of hydrogen which reacts is observed during the course of the reaction so that the reaction may be terminated before any reduction of the $C_{13}-C_{14}$ double bond to ethylene occurs.

The reaction between the bicyclo-octanes of general formula XII and (4-carboxybutylidene) triphenylphosphorane [obtained by the reaction of sodium methyl sulphanyl methylide with (4-carboxybutyl)triphenylphosphonium bromide] is carried out under the normal conditions utilized for effecting the Wittig reaction, e.g. in an inert solvent at ambient temperature. The reaction is preferably carried out in dimethyl sulphoxide because the phosphorane compound is practically insoluble in other solvents, e.g. tetrahydrofuran, and because a *cis*-double bond must be formed stereospecifically in the Wittig reaction. For the better performance of the Wittig reaction more than two molecular equivalents of the phosphorane compound are required for each mole of the bicyclo-octane reactant. The reaction is generally effected at a temperature of $10-40^\circ\text{C}$, preferably at $20-30^\circ\text{C}$, and is usually complete after about 30 minutes to four hours at laboratory temperature. The acid product of formula XXII may be extracted from the reaction mixture by conventional procedures and further purified by column chromatography on silica gel.

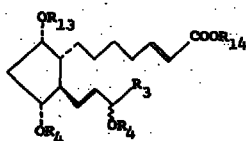
The lithiated amines of general formula XVII employed in the aforementioned process of the invention, for example lithium diisopropylamide, and benzene-selenenyl bromide and diphenyl diselenide can be prepared by known methods, for example as described in J. Amer. Chem. Soc., 95, 6139 (1973).

According to a further feature of the present invention, prostaglandin analogues of general formula VI, and their methyl esters, may also be prepared via compounds of general formulae IX (wherein R_6 represents the methyl radical or a straight- or branched-chain alkyl radical containing from 2 to 4 carbon atoms) and X, i.e. compounds of the general formula:



XXIII

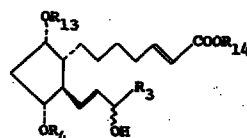
(wherein R_{12} represents a hydrogen atom, the methyl radical or a straight- or branched-chain alkyl radical containing from 2 to 4 carbon atoms, and the other symbols and $\sim$ are as hereinbefore defined) which may be prepared by the hydrolysis under alkaline conditions of a compound of the general formula:



XXIV

wherein R_{13} represents an alkanoyl group containing from 2 to 5 carbon atoms, R_{14} represents a straight- or branched-chain alkyl group containing from 1 to 4 carbon atoms and the other symbols and $\sim$ are as hereinbefore defined. The hydrolysis under alkaline conditions may be effected (1) with an aqueous solution of an alkali metal, e.g. sodium or potassium, hydroxide or carbonate in the presence of a water miscible solvent, e.g. tetrahydrofuran or an alkanol containing from 1 to 4 carbon atoms, to give compounds of general formula XXIII wherein R_{12} represents a hydrogen atom, or (2) with anhydrous potassium carbonate in an anhydrous alkanol containing from 1 to 4 carbon atoms, preferably absolute methanol, to give compounds of general formula XXIII wherein R_{12} represents an alkyl group containing from 1 to 4 carbon atoms.

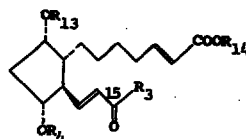
Compounds of general formula XXIV may be prepared from a compound of the general formula:



XXV

(wherein the various symbols and $\sim$ are as hereinbefore defined) by reaction with a dihydropyran 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.

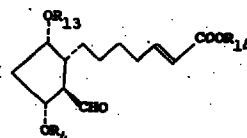
Compounds of general formula XXV may be prepared from a compound of the general formula:



XXVI

(wherein the various symbols and $\sim$ are as hereinbefore defined) by converting the 15-oxo group to a hydroxy group by methods known *per se*. The reduction is suitably effected (1) with excess sodium borohydride in an alcohol containing from 1 to 4 carbon atoms, e.g. methanol, at a low temperature, preferably at -30°C . to -60°C ., or (2) with zinc borohydride in a suitable inert organic solvent, e.g. 1,2-dimethoxyethane, at a temperature of -10°C . to 10°C . The product thus obtained is a mixture of isomers in which the 15-hydroxy group is in α - or β -configuration. If desired, the isomer having the hydroxy group in α -configuration may be separated from the isomer having the hydroxy group in β -configuration by column chromatography on silica gel. The separated isomers may be utilized in the procedures herein described to give prostaglandin analogues of general formula VI or methyl esters thereof in which the hydroxy group in position 15 is in α - or β -configuration.

Compounds of general formula XXVI may be prepared by the Wittig reaction of a compound of the general formula:

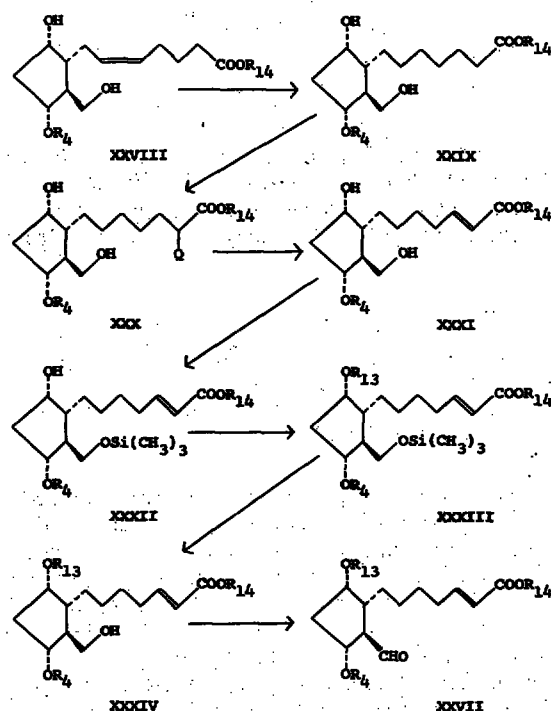


XXVII

(wherein the various symbols and $\sim$ are as hereinbefore defined) with the sodio derivative of a dialkyl phosphonate of general formula XIII wherein R_3 and R_4 are as hereinbefore defined. The reaction is preferably effected by suspending sodium hydride in an inert organic solvent, e.g. tetrahydrofuran or 1,2-dimethoxyethane, and adding the dialkyl phosphonate of general formula XIII. The resulting sodio derivative of the dialkyl phosphonate may then be reacted with the compound of general formula XXVII at a temperature of 20°C . to 45°C . to form the *trans*-enone compound of general formula XXVI stereoselectively.

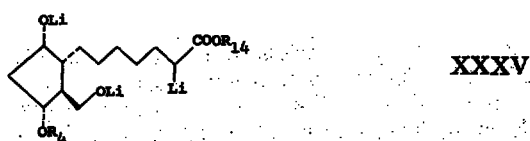
Compounds of general formula XXVII, wherein the various symbols and $\sim$ are as hereinbefore defined, may be prepared by a new synthetic route from known compounds of formula XXVIII, depicted hereafter, by the series of reactions depicted schematically below in Scheme A, wherein the various symbols are as hereinbefore defined.

SCHEME A

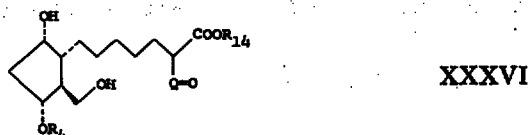


Compounds of general formula XXVIII may be reduced to give compounds of general formula XXIX. Suitably the reduction may be effected by hydrogenation in the presence of a hydrogenation catalyst, e.g. palladium on charcoal, palladium black or platinum dioxide, in an inert organic solvent, for example a lower alkanol, e.g. methanol or ethanol, at laboratory temperature at normal or elevated pressure, e.g. at a hydrogen pressure from atmospheric to 15 kg./cm².

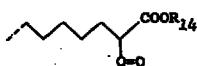
Compounds of general formula XXXI may be prepared by the process which comprises reacting compounds of general formula XXXIX with a compound of general formula XVII, wherein R₉ and R₁₀ are as hereinbefore defined, to obtain a lithium compound of the general formula:



(wherein R₄ and R₁₄ are as hereinbefore defined), reacting the lithium compound with benzeneselenenyl bromide (i.e. C₆H₅SeBr), or diphenyl diselenide, or a dialkyl disulphide or diphenyl disulphide of general formula R₁₁SSR₁₁, in which R₁₁ is as hereinbefore defined, hydrolysing the resulting intermediate to obtain compounds of general formula XXX, treating the resulting compound with hydrogen peroxide or sodium periodate, and decomposing the resulting compound of the general formula:



(wherein the various symbols are as hereinbefore defined) to convert the grouping



attached to the 8-position of the cyclopentane ring to a *trans*-Δ² grouping



wherein R_{14} is as hereinbefore defined.

The reaction between a compound of general formula XXIX and a lithiated amine of general formula XVII is carried out in an inert organic solvent, e.g. tetrahydrofuran, at a low temperature, e.g. at -78°C ., the ratio of the molecular equivalents of a compound of general formula XXIX to XVII in the reaction mixture being suitably adjusted to obtain a lithium compound of general formula XXXV.

The reaction between the lithium compound of general formula XXXV and benzeneselenenyl bromide, diphenyl diselenide or a dialkyl disulphide or diphenyl disulphide is preferably carried out in an inert organic solvent, e.g. tetrahydrofuran, hexamethylphosphoramide, diethyl ether, n-hexane or n-pentane or a mixture of two or more of them, at a low temperature, e.g. at -78°C .

The product of general formula XXX is converted to a compound of general formula XXXI by the procedure already described for the conversion of a compound of general formula XIX to a compound of general formula IX.

Compounds of general formula XXXII may be prepared by reacting compounds of general formula XXXI with trimethyl chlorosilane in an inert organic solvent, e.g. methylene chloride, in the presence of a base, e.g. pyridine or a tertiary amine, at a low temperature, e.g. at -30° to 0°C .

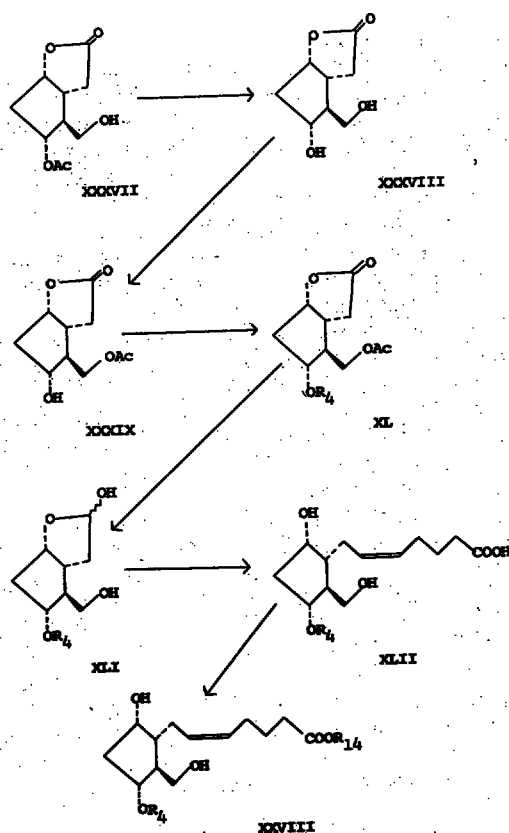
Compounds of general formula XXXIII may be prepared by reacting a trimethylsilyl ether of general formula XXXII with an appropriate acyl chloride or acid anhydride in an inert organic solvent, e.g. methylene chloride, in the presence of a base, e.g. pyridine or a tertiary amine, at a low temperature, e.g. at 0° to 30°C .

Compounds of general formula XXXIV may be prepared by treating compounds of general formula XXXIII by methods known *per se* for the removal of the trimethylsilyl group, for example by treatment with an acid: it is preferable not to use a strong acid in order to avoid the risk of the removal of the group R_4 .

Compounds of general formula XXXIV may be converted to compounds of general formula XXVII under mild and neutral conditions, for example with chromium trioxide-pyridine complex or Jones' reagent at a moderately low temperature.

Compounds of general formula XXVIII used as starting material in the series of reactions depicted in Scheme A may be prepared by the methods described in Japanese Patent Publication No. 49-102646 from the known compound of formula XXXVII [prepared as described in J. Amer. Chem. Soc., 91, 5675 (1969) and *ibid*, 92, 397 (1970)] by the series of reactions depicted schematically below in Scheme B, wherein Ac represents the acetyl group and the other symbols are as hereinbefore defined.

SCHEME B



Compounds of formula XXXVIII may be prepared by hydrolysis under alkaline conditions of compounds of formula XXXVII, for example using potassium carbonate in methanol. Compounds of formula XXXIX may be obtained by the acetylation of compounds of formula XXXVIII under mild conditions and may be converted to compounds of general formula XL by reaction with a dihydropyran, 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. Compounds of general formula XLI may be prepared by reducing compounds of general formula XL with diisobutylaluminium hydride in toluene at a temperature below -60°C . Dimethyl anion, previously prepared from sodium hydride and dimethyl sulphoxide, is reacted with (4-carboxy-butyl)triphenylphosphonium bromide to form (4-carboxy-butylidene)triphenylphosphorane. To that compound is added a compound of general formula XLI and the mixture in dimethyl sulphoxide is made to react at room temperature to yield compounds of general formula XLII. The acids of general formula XLII are then esterified by methods known *per se*, for example by reaction with a diazoalkane to give compounds of general formula XXVIII.

Methyl esters of the *trans*- Δ^2 -prostaglandins of general formula VI can be obtained by reaction of the acids with (i) diazomethane, (ii) methanol in the presence of dicyclohexylcarbodiimide as a condensing agent, or (iii) methanol 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. British Patents Nos. 1,362,956 and 1,364,125).

Compounds of general formula VI may, if desired, be converted by methods known *per se* into 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 VI are not vitiated by side-effects ascribable to those cations. Preferably the salts are water-soluble. Suitable salts include the alkali metal, e.g. sodium and potassium, 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.

The non-toxic salts may be prepared from acids of general formula VI by, for example, reaction of stoichiometric quantities of an acid of general formula VI and the appropriate base, e.g. an alkali metal hydroxide or carbonate, ammonium hydroxide, ammonia or an 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 *trans*- Δ^2 -prostaglandin analogues of general formula VI and methyl esters thereof may, if desired, be converted into cyclodextrin clathrates. The clathrates may be prepared by dissolving the cyclodextrin in water and/or an organic solvent which is miscible with water and adding to the solution the prostaglandin compound 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 decanting. 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 compounds.

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

REFERENCE EXAMPLE 1

Synthesis of (2-carboxyethyl)triphenylphosphonium bromide

A solution of 90 g. of triphenylphosphine and 50 g. of 3-bromopropionic acid in 550 ml. of acetonitrile was refluxed for two days. The reaction mixture was then distilled under reduced pressure to remove acetonitrile, and the residue was stirred well together with diethyl ether, and then the upper ethereal layer removed by decantation. The operation was repeated twice to form the crystalline product, which was recrystallised from acetonitrile; yield of the title compound: 115 g, m.p. 195—198°C.

IR (potassium bromide tablet): 2880, 1740, 1434, 1382, 1322, 1230, 1105, 745, 690, 520 and 505 cm^{-1} .

REFERENCE EXAMPLE 2

Synthesis of 9 α -hydroxy-11 α ,15 α -bis-(2-tetrahydropyranyloxy)-16,16-dimethyl-2,3-dinorprost-*trans*-13-enoic acid

A solution of 92 g. of (2-carboxyethyl)triphenylphosphonium bromide (prepared as described in Reference Example 1) in 200 ml. of dimethyl sulphoxide was mixed with 200 ml. of a 2.1M solution of sodiummethylsulphinylmethylide in dimethyl sulphoxide whilst maintaining the temperature at 25°C. To the resulting red mixture was added 150 ml. of a solution containing 34 g. of 2-oxa-6-*syn*-(3 α -2'-tetrahydropyranyloxy-4,4-dimethyl-oct-*trans*-1-enyl)-7-*anti*-(2-tetrahydropyranyloxy)-*cis*-bicyclo[3,3,0]octan-3-ol [prepared as described in British Patent Specification No. 1,398,291, Preparation 6] in dimethyl sulphoxide. The resulting mixture was stirred for 2 hours at 25°C. and 1 hour at 40°C., and then poured into a mixture of 3.5 litres of ice-water, 500 ml. of diethyl ether and 6 g. of potassium carbonate, and extracted with ethyl acetate. The aqueous layer was extracted three times with a mixture of diethyl ether and ethyl acetate (1:1) to remove the neutral substances. The aqueous layer was adjusted to pH 2 with oxalic acid and extracted 4 times with a diethyl ether-pentane mixture (1:1), and the extract was washed with water, dried and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using an ethanol-benzene mixture (1:20) as eluant to give 9 α -hydroxy-11 α ,15 α -bis-(2-tetrahydropyranyloxy)-16,16-dimethyl-2,3-dinorprosta-*cis*-(and *trans*)-5,*trans*-13-dienoic acids as a colorless oil in a yield of 12 g. TLC (developing solvent, methylene chloride: methanol=19:1): R_f=0.21.

The product was dissolved in 300 ml. of methanol, mixed with 4 g. of 5% palladium on carbon and treated with an equimolar amount of hydrogen at room temperature. The reaction mixture was filtered with a glass filter to remove the catalyst and the filtrate concentrated under reduced pressure to yield the title compound (12 g.). TLC (developing solvent, methylene chloride: methanol=19:1): $R_f=0.21$.

REFERENCE EXAMPLE 3

Synthesis of 9 α -hydroxy-11 α ,15 α -bis-(2-tetrahydropyranyloxy)-17(ξ),20-diethyl-2,3-dinorprost-*trans*-13-enoic acid

Following the same procedure as described in Reference Example 2 but using 16 g. of 2-oxa-6-*syn*-(3 α -2'-tetrahydropyranyloxy-5(ξ)-ethyl-dec-*trans*-1-enyl)-7-*anti*-(2-tetrahydropyranyloxy)-*cis*-bicyclo[3,3,0]octan-3-ol as starting material, the title compound (5.6 g.) was obtained. TLC (developing solvent, methylene chloride: methanol=19:1): $R_f=0.23$.

The starting material was synthesized as follows:

65 g. of dimethyl methylphosphonate were dissolved in 465 ml. of tetrahydrofuran and the solution cooled to -70°C . in a nitrogen atmosphere. The solution of butyl lithium produced from 85.3 g. of butyl bromide and 10.7 g. of lithium in 400 ml. of diethyl ether was added dropwise into the other prepared solution during about 15 minutes at a temperature below -50°C . After stirring for 10 minutes, 44 g. of ethyl 3(ξ)-ethyloctanoate in 140 ml. of tetrahydrofuran was added dropwise at a temperature below -50°C ., the mixture was stirred at the same temperature for 2 hours and then at room temperature for a further 2 hours and then 92 g. of acetic acid were added. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in water, extracted with diethyl ether, and the ether extract was washed with water, dried over magnesium sulphate and concentrated under reduced pressure. The residue was distilled under reduced pressure. 55 g. of dimethyl 2-oxo-4(ξ)-ethylnonylphosphonate (b.p. $113-121^\circ\text{C}/0.2$ mm Hg.) was obtained as a colorless oil.

IR (liquid film): 2950, 2860, 1710, 1455, 1270, 1190, 1040 and 820 cm^{-1} .

9.42 g. of sodium hydride (purity 50%) were suspended in 1.55 litres of tetrahydrofuran, and 55 g. of the compound previously obtained in 210 ml. of tetrahydrofuran were added to the suspension, and the mixture stirred at room temperature. When the evolution of hydrogen ceased and the suspension became transparent, 41.5 g. of 2-oxa-6-*syn*-formyl-7-*anti*-acetoxy-*cis*-bicyclo[3,3,0]octan-3-one in 520 ml. of tetrahydrofuran were added, the mixture was stirred at room temperature for 2 hours and then acidified with glacial acetic acid to pH 4 and the formed precipitate was filtered off. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography using benzene-ethyl acetate (5:1) as eluent. 62 g. of 2-oxa-6-*syn*-(3-oxo-5(ξ)-ethyldec-*trans*-1-enyl)-7-*anti*-acetoxy-*cis*-bicyclo[3,3,0]octan-3-one were obtained.

TLC (developing solvent, benzene: diethyl ether: methanol=5:1:1): $R_f=0.71$;

IR (liquid film): 2950, 2930, 2860, 1775, 1740, 1690, 1665, 1620, 1240, 1170 and 980 cm^{-1} ;

NMR (CCl₄ solution): 6.50—5.80 (2H, m), 5.10—4.70 (2H, m), 2.02 (3H, s), 1.10—0.60 (6H, m).

62 g. of the compound thus obtained were dissolved in 600 ml. of 1,2-dimethoxyethane, and reduced with 180 ml. of a solution of 0.55M zinc borohydride in 1,2-dimethoxyethane at 20°C . for 30 minutes and the crude product was purified by silica gel column chromatography using diethyl ether-hexane-ethyl acetate (2:1:1) as eluent. 12.5 g. of 2-oxa-6-*syn*-(3 α -hydroxy-5(ξ)-ethyldec-*trans*-1-enyl)-7-*anti*-acetoxy-*cis*-bicyclo[3,3,0]octan-3-one were obtained.

TLC (developing solvent, methylene chloride: methanol=19:1): $R_f=0.52$;

IR (liquid film): 3460, 2950, 2870, 1770, 1740, 1370, 1240, 1180 and 975 cm^{-1} ;

NMR (CCl₄ solution): 5.50—5.30 (2H, m), 5.10—4.60 (2H, m), 4.10—3.80 (1H, m), 2.03 (3H, s), 1.10—0.45 (6H, m).

12.5 g. of the compound thus obtained were hydrolyzed with an equimolar amount of potassium carbonate in methanol at 25°C . for 15 minutes to obtain 10.8 g. of 2-oxa-6-*syn*-(3 α -hydroxy-5(ξ)-ethyldec-*trans*-1-enyl)-7-*anti*-hydroxy-*cis*-bicyclo[3,3,0]octan-3-one as a pale yellow oil.

TLC (developing solvent, methylene chloride: methanol=19:1): $R_f=0.30$.

IR (liquid film): 3400, 2950, 2860, 1775, 1180, 1090, 1040 and 975 cm^{-1} ;

NMR (CDCl₃ solution): 5.50—5.30 (2H, m), 5.00—4.60 (1H, m), 4.10—3.60 (4H, m), 1.05—0.40 (6H, m).

10.8 g. of the compound thus obtained were dissolved in 95 ml. of methylene

17

17

chloride and to the solution was added three times the molar quantity of dihydropyran (in relation to the compound) in the presence of a trace amount of *p*-toluene-sulphonic acid at 25°C. for 15 minutes to obtain 17 g. of 2 - oxa - 6 - syn - (3 α - 2' - tetrahydropyranyloxy - 5(ξ) - ethyldec - trans - 1 - enyl) - 7 - anti - (2 - tetrahydropyranyloxy) - cis - bicyclo[3,3,0]octan - 3 - one.

TLC (developing solvent, methylene chloride: methanol=19:1): Rf=0.74;

IR (liquid film): 2930, 2860, 1775, 1120, 1080, 1040, 1025 and 980 cm⁻¹;

NMR (CDCl₃ solution): 5.50—5.20 (2H, m), 5.10—4.70 (1H, m), 4.70—4.40 (2H, m), 1.05—0.45 (6H, m).

17 g. of the compound thus obtained were reduced with twice the molar quantity of diisobutylaluminium hydride (in relation to the compound) in toluene at -60°C. for 30 minutes to obtain 16 g. of 2 - oxa - 6 - syn - (3 α - 2' - tetrahydropyranyloxy - 5(ξ) - ethyldec - trans - 1 - enyl) - 7 - anti - (2 - tetrahydropyranyloxy) - cis - bicyclo[3,3,0]octan - 3 - ol.

TLC (developing solvent, methylene chloride: methanol=19:1): Rf=0.39;

IR (liquid film): 3420, 2950, 2860, 1120, 1080, 1040, 1020 and 980 cm⁻¹;

NMR (CDCl₃ solution): 5.70—5.20 (2H, m), 4.70—4.30 (3H, m), 1.10—0.45 (6H, m).

REFERENCE EXAMPLE 4

Synthesis of methyl 9 α -hydroxy-11 α ,15 α -bis-(2-tetrahydropyranyloxy)-16,16-dimethyl-2,3-dinorprost-trans-13-enoate

To a solution of 6 g. of 9 α - hydroxy - 11 α ,15 α - bis - (2 - tetrahydropyranyloxy) - 16,16 - dimethyl - 2,3 - dinorprost - trans - 13 - enoic acid (prepared as described in Reference Example 2) in 100 ml. of diethyl ether was added a freshly prepared solution of diazomethane in diethyl ether until the reaction mixture became yellow. The reaction mixture was then concentrated under reduced pressure at a low temperature, and the residue purified by means of silica gel column chromatography using an ethyl acetate-cyclohexane mixture (1:1) as eluent to yield 4.92 g. of the title compound as a colorless oil.

TLC (developing solvent, ethyl acetate: cyclohexane=1:1): Rf=0.59.

REFERENCE EXAMPLE 5

Synthesis of methyl 9 α -hydroxy-11 α ,15 α -bis-(2-tetrahydropyranyloxy)-17(ξ),20-diethyl-2,3-dinorprost-trans-13-enoate

By the same procedure as described in Reference Example 4, 4.7 g. of the title compound (in the form of a colorless oil) were obtained from 5.6 g. of 9 α - hydroxy - 11 α ,15 α - bis - (2 - tetrahydropyranyloxy) - 17(ξ),20 - diethyl - 2,3 - dinorprost - trans - 13 - enoic acid (prepared as mentioned in Reference Example 3).

TLC (developing solvent, ethyl acetate: cyclohexane=1:1): Rf=0.59;

IR (liquid film): 3400, 2940, 2860, 1740, 1080, 1020 and 980 cm⁻¹;

NMR (CDCl₃ solution): 5.70—5.50 (2H, m), 4.70—4.50 (2H, m), 3.65 (3H, s), 1.10—0.45 (6H, m).

REFERENCE EXAMPLE 6

Synthesis of 9 α -hydroxy-11 α ,15 α -bis-(2-tetrahydropyranyloxy)-16,16-dimethyl-2,3-dinorprost-trans-13-enaldehyde

A solution of 8 g. of the product of Reference Example 4 in 230 ml. of toluene was cooled to -65°C., mixed with 34 ml. of toluene solution containing diisobutylaluminium hydride (25% w/v), and the reaction mixture stirred for 30 minutes at the same temperature. Methanol was gradually added dropwise and, after the bubbling stopped, the resulting mixture was raised to 0°C., then stirred with 50 ml. of water for 30 minutes. The aluminium hydroxide which formed was filtered off, and the filtrate was washed with aqueous sodium chloride solution, dried over magnesium sulphate and concentrated at reduced pressure to obtain the title compound as a colorless oil: yield 8 g.

TLC (developing solvent, ethyl acetate: cyclohexane=1:1): Rf=0.44.

REFERENCE EXAMPLE 7

Synthesis of 9 α -hydroxy-11 α ,15 α -bis-(2-tetrahydropyranyloxy)-17(ξ),20-diethyl-2,3-dinorprost-trans-13-enaldehyde

By the same procedure as described in Reference Example 6, 4.4 g. of the title compound (in the form of a colorless oil) were obtained from 4.7 g. of the product of Reference Example 5.

TLC (developing solvent, ethyl acetate: cyclohexane=1:1): Rf=0.51

REFERENCE EXAMPLE 8

Synthesis of ethyl 9 α -hydroxy-11 α ,15 α -bis-(2-tetrahydrofuran-2-yl)-16,16-dimethylprosta-*trans*-2,trans-13-dienoate

To a mixture of 1.02 g. of sodium hydride (purity 65%) and 110 ml. of tetrahydrofuran was added dropwise, with stirring, 6.2 g. of triethylphosphonoacetate, the reaction mixture being maintained at a temperature less than 30°C. Stirring was continued at 25°C. for 30 minutes until the evolution of hydrogen stopped. 4 g. of the product of Reference Example 6 in 135 ml. of tetrahydrofuran were added thereto, and the resulting mixture was stirred for 50 minutes at 25°C., adjusted to pH 7 with acetic acid, diluted with water, extracted with diethyl ether and the ethereal extract washed with water, dried and concentrated. The residue was purified by silica gel column chromatography using an ethyl acetate-cyclohexane mixture (1:3) as eluent to obtain 4 g. of the title compound as a colorless oil.

TLC (developing solvent, ethyl acetate: cyclohexane=1:1): R_f=0.55.

REFERENCE EXAMPLE 9

Synthesis of methyl 9 α -hydroxy-11 α ,15 α -bis-(2-tetrahydropyranyloxy)-17(ϵ),20-diethylprosta-*trans*-2,trans-13-dienoate

By the same procedure as described in Reference Example 8, but replacing the triethylphosphonoacetate by trimethylphosphonoacetate, 4.8 g. of the title compound (in the form of a colorless oil) were obtained from 4.7 g. of the product of Reference Example 7.

TLC (developing solvent, ethyl acetate: cyclohexane=1:1): R_f=0.66;

IR (liquid film): 3440, 2930, 2850, 1730, 1655, 1435, 1140, 1085, 1030 and 985 cm⁻¹.

REFERENCE EXAMPLE 10

Synthesis of 9-oxo-11 α ,15 α -bis-(2-tetrahydropyranyloxy)-16,16-dimethylprosta-*trans*-2,trans-13-dienoic acid

4 g. of ethyl 9 α -hydroxy-11 α ,15 α -bis-(2-tetrahydropyranyloxy)-16,16-dimethylprosta-*trans*-2,trans-13-dienoate (prepared as described in Reference Example 8) were dissolved in 130 ml. of a mixture of ethanol and water (3:1), mixed with 3.9 g. of potassium hydroxide and stirred at 25°C. for 2 hours. The reaction mixture was then acidified with an aqueous solution of oxalic acid to pH 5, diluted with 100 ml. of water and extracted with ethyl acetate. The extracts were washed with water, dried over sodium sulphate and concentrated under reduced pressure to obtain 3.88 g. of 9 α -hydroxy-11 α ,15 α -bis-(2-tetrahydropyranyloxy)-16,16-dimethylprosta-*trans*-2,trans-13-dienoic acid.

TLC (developing solvent, ethyl acetate: cyclohexane=1:1): R_f=0.18.

2.46 g. of the obtained compound were dissolved in 72 ml. of diethyl ether and the solution stirred at 3°C. A solution of 15 g. of manganese sulphate, 3.1 g. of chromium trioxide, 72 ml. of water and 3.5 ml. of sulphuric acid was added. After stirring for 3.5 hours at 3°C., the reaction mixture was extracted with diethyl ether. The organic layer was washed with water, dried over sodium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate-benzene (1:1) as eluent to give 2.35 g. of the title compound having the following physical characteristics.

TLC (developing solvent, methylene chloride: methanol=20:1): R_f=0.24;

IR (liquid film): 2925, 2850, 1740, 1690, 1645, 1445, 1375, 1350, 1240, 1140, 1090, 1045 and 980 cm⁻¹.

REFERENCE EXAMPLE 11

Synthesis of 9-oxo-11 α ,15 α -bis-(2-tetrahydropyranyloxy)-17(ϵ),20-diethylprosta-*trans*-2,trans-13-dienoic acid

By the same procedure as described in Reference Example 10, 676 mg. of the title compound were obtained from 1.31 g. of methyl 9 α -hydroxy-11 α ,15 α -bis-(2-tetrahydropyranyloxy)-17(ϵ),20-diethylprosta-*trans*-2,trans-13-dienoate prepared as mentioned in Reference Example 9).

TLC (developing solvent, methylene chloride: methanol=20:1): R_f=0.22;

IR (liquid film): 2930, 2840, 1740, 1690, 1645, 1450, 1375, 1350, 1240, 1140, 1085, 1045, 1035 and 980 cm⁻¹;

NMR (CDCl₃ solution): 9.40 (1H, broad s), 7.05 (1H, dt), 5.80 (1H, d), 5.85—5.30 (2H, m), 5.00—4.50 (2H, m), 4.50—3.20 (6H, m).

EXAMPLE 1

Synthesis of 16,16-dimethyl-*trans*-2,3-didehydro-PGE₁ [9-oxo-11 α ,15 α -dihydroxy-16,16-dimethylprosta-*trans*-2,*trans*-13-dienoic acid]

2.35 g. of the bis-tetrahydropyranyl ether prepared as described in Reference Example 10 were dissolved in 6 ml. of tetrahydrofuran and 60 ml. of a 65% (v/v) aqueous acetic acid solution and the solution stirred at 60° to 70°C. for 20 minutes. The reaction mixture was then extracted with ethyl acetate, and the organic layer was washed with water, dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate-cyclohexane (2:3) as eluent to yield 270 mg. of the title compound.

TLC (developing solvent, tetrahydrofuran:chloroform:acetic acid=2:10:1): R_f=0.30;

IR (liquid film): 3400, 2930, 1740, 1695, 1650, 980, 870 and 850 cm⁻¹;

NMR (CDCl₃ solution): 7.2—6.8 (1H, m), 6.6—5.37 (6H, m), 5.03—4.7 (1H, m).

EXAMPLE 2

Synthesis of 17(ξ),20-diethyl-*trans*-2,3-didehydro-PGE₁ [9-oxo-11 α ,15 α -dihydroxy-17(ξ),20-diethylprosta-*trans*-2,*trans*-13-dienoic acid]

By the same procedure as described in Example 1, 313 mg. of the title compound were obtained from 676 mg. of the bis-tetrahydropyranyl ether prepared as mentioned in Reference Example 11.

TLC (developing solvent, tetrahydrofuran:chloroform:acetic acid: 2:10:1):

R_f=0.28;

IR (liquid film): 3350, 2930, 2850, 1745, 1700, 1655, 1460, 1420, 1385, 1170, 1090 and 985 cm⁻¹;

NMR (CDCl₃ solution): 6.99 (1H, dt), 5.78 (1H, d), 5.90 (3H, broad s), 5.70—5.40 (2H, m), 4.40—3.78 (2H, m), 2.95—2.55 (1H, dd).

EXAMPLE 3

Synthesis of 16,16-dimethyl-*trans*-2,3-didehydro-PGE₁ methyl ester

50.8 mg. of 16,16-dimethyl-*trans*-2,3-didehydro-PGE₁ (prepared as described in Example 1) were dissolved in 3 ml. of diethyl ether, and to the solution a freshly prepared ethereal solution of diazomethane was added so that the reaction mixture turned yellow. The reaction mixture was concentrated under reduced pressure at a low temperature, and the residue purified by column chromatography on silica gel using ethyl acetate-cyclohexane (1:3) as eluent to give 40 mg. of the title compound.

TLC (developing solvent, chloroform:tetrahydrofuran:acetic acid=10:2:1):

R_f 0.51;

IR (liquid film): 3400, 2940, 2850, 1750, 1730, 1660, 1440, 1280 cm⁻¹;

NMR (CDCl₃ solution): 7.10—6.75 (1H, m), 5.95—5.40 (3H, m), 3.71 (3H, s), 4.20—3.60 (2H, m), 2.75 (1H, dd), 1.00—0.75 (9H, m).

EXAMPLE 4

Synthesis of 17(ξ),20-diethyl-*trans*-2,3-didehydro-PGE₁ methyl ester

By the same procedure as described in Example 3, 97 mg. of the title compound were obtained from 130 mg. of the 17(ξ),20-diethyl-*trans*-2,3-didehydro-PGE₁ (prepared as mentioned in Example 2).

TLC (developing solvent, chloroform:tetrahydrofuran:acetic acid=10:2:1):

R_f 0.33;

IR (liquid film): 3470, 2920, 2840, 1735, 1720, 1650, 1450, 1430, 1270, 1165, 1080 and 980 cm⁻¹;

NMR (CDCl₃ solution): 6.93 (1H, dt), 5.79 (1H, d), 5.67—5.40 (2H, m), 4.37—3.83 (2H, m), 3.71 (3H, s), 2.92—2.53 (1H, dd), 1.06—0.65 (6H, m).

REFERENCE EXAMPLE 12

Methyl 9 α -hydroxy-11 α ,15 α -bis-(2-tetrahydropyranyloxy)-17(ξ),20-diethylprosta-*trans*-2,*trans*-13-dienoate

A solution of 1030 mg. of diisopropylamine in 22 ml. of tetrahydrofuran was cooled to -70°C., and to it 7.9 ml. of a solution of n-butyllithium in hexane (1.3 molar concentration) were added dropwise and stirred for 15 minutes at -70°C. to give lithium diisopropylamide.

To the lithium diisopropylamide solution, 2.37 g. of methyl 9 α -hydroxy-11 α ,15 α -bis-(2-tetrahydropyranyloxy)-17(ξ),20-diethylprost-*trans*-13-enoate in 11 ml. of tetrahydrofuran were added dropwise at -70°C. and the reaction mixture stirred for 30 minutes at the same temperature. A solution of 1.83 g. of diphenyl diselenide in

11 ml. of tetrahydrofuran was added dropwise to the reaction mixture at -70°C . and stirring was continued for 1 hour at the same temperature and then for 30 minutes at room temperature. The reaction mixture was poured into a small amount of a saturated aqueous solution of ammonium chloride, and extracted with 175 ml. of ethyl acetate. The organic layer was washed with a small amount of 1N hydrochloric acid and a saturated aqueous solution of sodium bicarbonate. Maintaining the temperature below 30°C ., 3.1 ml. of 30% hydrogen peroxide were added dropwise and the reaction mixture stirred for 1 hour at 28°C . The reaction mixture was then washed successively with water, a saturated aqueous solution of sodium carbonate and a saturated solution of sodium chloride, dried over anhydrous magnesium sulphate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using cyclohexane-ethyl acetate (3:1) as eluent to give 1.31 g. (70.3%) of the title compound having the following physical characteristics:—

IR (liquid film): 3440, 2930, 2850, 1730, 1655, 1435, 1140, 1085, 1030, and 985 cm^{-1} ;

NMR (CDCl_3 solution): 6.95 (1H, dt), 5.79 (1H, d), 5.80—5.15 (2H, m), 4.90—4.50 (2H, m), 3.71 (3H, s);

TLC (developing solvent, ethyl acetate: benzene=1:2): $R_f=0.50$.

The methyl 9 α -hydroxy-11 α ,15 α -bis-(2-tetrahydropyranyloxy)-17(ϵ),20-diethylprost-*trans*-13-enoate used as starting material in the procedure described above was prepared by esterification of the corresponding acid, 9 α -hydroxy-11 α ,15 α -bis-(2-tetrahydropyranyloxy)-17(ϵ),20-diethylprost-*trans*-13-enoic acid using an ethereal solution of diazomethane. The said acid was prepared by a procedure similar to that described in J. Amer. Chem. Soc. 92, 2586 (1970) for the preparation of 9 α -hydroxy-11 α ,15 α -bis-(2-tetrahydropyranyloxy)-prost-*trans*-13-enoic acid.

REFERENCE EXAMPLE 13

Methyl 9 α -hydroxy-11 α ,15 α -bis-(2-tetrahydropyranyloxy)-16,16-dimethylprosta-*trans*-2,*trans*-13-dienoate

By the same procedure as described in Reference Example 12 2.33 g. (68%) of the title compound were obtained from 3.42 g. of methyl 9 α -hydroxy-11 α ,15 α -bis-(2-tetrahydropyranyloxy)-16,16-dimethylprost-*trans*-13-enoate. The title compound has the following physical characteristics:—

IR (liquid film): 3450, 2930, 2850, 1725, 1660, 1440, 1140, 1080, and 980 cm^{-1} ;

TLC (developing solvent, benzene: cyclohexane=1:1): $R_f=0.55$.

The methyl 9 α -hydroxy-11 α ,15 α -bis-(2-tetrahydropyranyloxy)-16,16-dimethylprost-*trans*-13-enoate used as starting material in the procedure described above was prepared by esterification of the corresponding acid, 9 α -hydroxy-11 α ,15 α -bis-(2-tetrahydropyranyloxy)-16,16-dimethylprost-*trans*-13-enoic acid using an ethereal solution of diazomethane. The said acid was prepared by a procedure similar to that described in J. Amer. Chem. Soc. 92, 2586 (1970) for the preparation of 9 α -hydroxy-11 α ,15 α -bis-(2-tetrahydropyranyloxy)-prost-*trans*-13-enoic acid.

REFERENCE EXAMPLE 14

9-Oxo-11 α ,15 α -bis-(2-tetrahydropyranyloxy)-17(ϵ),20-diethylprosta-*trans*-2,*trans*-13-dienoic acid

1.31 g. of methyl 9 α -hydroxy-11 α ,15 α -bis-(2-tetrahydropyranyloxy)-17(ϵ),20-diethylprosta-*trans*-2,*trans*-13-dienoate (prepared as described in Reference Example 12) were dissolved in a mixture of 10 ml. of ethanol, 2 ml. of water and 400 mg. of potassium hydroxide and the solution was stirred at below 50°C . for 2 hours. The reaction mixture was acidified with aqueous sulphuric acid and diluted with ethyl acetate. The organic layer was washed with water, dried over sodium sulphate and concentrated under reduced pressure to obtain 1.3 g. of 9 α -hydroxy-11 α ,15 α -bis-(2-tetrahydropyranyloxy)-17(ϵ),20-diethylprosta-*trans*-2,*trans*-13-dienoic acid having the following physical characteristics:—

IR (liquid film): 3440, 2940, 2850, 1740, 1720, 1655, 1380, 1245, 1090, 1035, 985 and 920 cm^{-1} ;

NMR (CDCl_3): 6.95 (1H, dt), 6.51 (2H, broad s), 5.79 (1H, d), 5.70—5.10 (2H, m), 4.90—4.50 (2H, m);

TLC (developing solvent, methylene chloride: methanol=20:1): $R_f=0.41$.

811 mg. of the 9 α -hydroxy-11 α ,15 α -bis-(2-tetrahydropyranyloxy)-17(ϵ),20-diethylprosta-*trans*-2,*trans*-13-dienoic acid obtained were dissolved in 38 ml. of diethyl ether and the solution stirred at 0°C . A solution of manganese sulphate (6.8 g.), 1.5 g. of chromium trioxide, 34 ml. of water and 1.6 ml. of sulphuric acid was added. After

stirring for 1.5 hours at 0 to 5°C., the reaction mixture was extracted with ethyl acetate. The organic extract was washed with water, dried over sodium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate-benzene (1:1) as eluent to give 676 mg. of the title compound having the same physical characteristics as the product of Reference Example 11.

REFERENCE EXAMPLE 15

9-Oxo-11 α ,15 α -bis-(2-tetrahydropyranyloxy)-16,16-dimethylprosta-*trans*-2,*trans*-13-dienoic acid

By the same procedure as described in Reference Example 14, 2.35 g. of the title compound were obtained from 3.95 g. of methyl 9 α -hydroxy-11 α ,15 α -bis-(2-tetrahydropyranyloxy)-16,16-dimethylprosta-*trans*-2,*trans*-13-dienoate (prepared as described in Reference Example 13). The title compound has the same physical characteristics as the product of Reference Example 10.

EXAMPLE 5

17(ξ),20-Diethyl-*trans*-2,3-didehydro-PGE₁

676 mg. of the bis-tetrahydropyranyl ether prepared as described in Reference Example 14 were dissolved in a mixture of 0.5 ml. of tetrahydrofuran and 5 ml. of 65% (v/v) aqueous acetic acid and the solution stirred at 60 to 70°C. for 20 minutes. The reaction mixture was extracted with ethyl acetate, and the organic layer was washed with water, dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate-cyclohexane (2:3) as eluent to yield 313 mg. of the title compound having the same physical characteristics as the product of Example 2.

EXAMPLE 6

16,16-Dimethyl-*trans*-2,3-didehydro-PGE₁

By the same procedure as described in Example 5, 270 mg. of the title compound were obtained from 2.35 g. of the bis-tetrahydropyranyl ether prepared as described in Reference Example 15. The title compound has the same physical characteristics as the product of Example 1.

EXAMPLE 7

16,16-Dimethyl-*trans*-2,3-didehydro-PGE₁ methyl ester

50.8 mg. of 16,16-dimethyl-*trans*-2,3-didehydro-PGE₁ (prepared as described in Example 6) were dissolved in 3 ml. of diethyl ether, and to the solution a freshly prepared ethereal solution of diazomethane was added so that the reaction mixture turned yellow. The reaction mixture was concentrated under reduced pressure at low temperature, and the residue purified by column chromatography on silica gel using ethyl acetate-cyclohexane (1:3) as eluent to give 40 mg. of the title compound having the same physical characteristics as the product of Example 3.

REFERENCE EXAMPLE 16

2 α -(6-Methoxycarbonylhexyl)-3 β -hydroxymethyl-4 α -(2-tetrahydropyranyloxy)-cyclopentan-1 α -ol

14.2 g. of 2 α -(6-methoxycarbonylhex-*cis*-2-enyl)-3 β -hydroxymethyl-4 α -(2-tetrahydropyranyloxy)cyclopentan-1 α -ol (prepared as described hereinafter) was hydrogenated at a pressure of one atmosphere in 300 ml. of methanol containing 3 g. of 5% (w/w) palladium on charcoal. The reduction was stopped after the absorption of one equivalent of hydrogen. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to give 13.8 g of the title compound having the following physical characteristics:—

TLC (developing solvent, benzene: ethyl acetate=1:1): R_f=0.28;

IR (liquid film): 3450, 1740, 1440, 1030 cm⁻¹;

NMR (CDCl₃ solution): 5.00—4.55 (1H, m), 3.70 (3H, s).

2 α -(6-Methoxycarbonylhex-*cis*-2-enyl)-3 β -hydroxymethyl-4 α -(2-tetrahydropyranyloxy)cyclopentan-1 α -ol, used as a starting material in the above procedure, was prepared from 2-oxa-3-oxo-6-*syn*-hydroxymethyl-7-*anti*-acetoxy-*cis*-bicyclo[3,3,0]octane, [prepared as described by E. J. Corey *et al.*, J. Amer. Chem. Soc., 92, 397 (1970)] as follows:—

190 g. of 2-oxa-6-*syn*-hydroxymethyl-7-*anti*-acetoxy-*cis*-bicyclo[3,3,0]octan-3-one in 1.5 litres of absolute methanol and 130 g. of potassium hydroxide were stirred at room temperature for one hour, and then successively cooled in an ice-bath, and neutralized with hydrochloric acid. The precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was washed

with ethanol, and then with ethyl acetate, and dried to give 124 g. of 2 - oxa - 6 - *syn* - hydroxymethyl - 7 - *anti* - hydroxy - *cis* - bicyclo[3,3,0]octan - 3 - one as white crystallites having the following physical characteristics:—

m.p. 119°C.;

IR (KBr tablet): 3350, 2970—2880, 1740, 1480, 1440, 1410, 1380, 1335, 1305, 1270, 1205, 1100, 1080, 1060, 1040, 1020, 1000 and 975 cm^{-1} ;

NMR (CDCl_3 + deuterio dimethyl sulphoxide solution): 5.10—4.60 (1H, m), 4.29 (2H, s), 4.13—3.77 (1H, m) and 3.38 (2H, d);

TLC (developing solvent, methylene chloride: methanol=20:1): R_f =0.27.

124 g. of 2 - oxa - 6 - *syn* - hydroxymethyl - 7 - *anti* - hydroxy - *cis* - bicyclo[3,3,0]octan - 3 - one (obtained as described above) were dissolved in absolute pyridine (1.4 litres) and cooled to -40°C . 74 g. of acetic anhydride were added dropwise and the mixture stirred for 5 hours at -40° to -20°C . and then for 16 hours at 0°C . The pyridine was evaporated off under reduced pressure and the residue was dissolved in 1 litre of ethyl acetate. 200 g. of sodium bisulphate were added, and the mixture stirred vigorously and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using a benzene-ethyl acetate mixture (1:3) as eluent to give 112 g. of 2 - oxa - 6 - *syn* - acetoxy-methyl - 7 - *anti* - hydroxy - *cis* - bicyclo[3,3,0]octan - 3 - one as colourless needles having the following physical characteristics:—

m.p.: 36° to 37°C .;

IR (KBr tablet): 3450, 2960, 2850, 1775, 1740, 1420, 1370, 1250, 1190, 1120, 1090, 1040 and 980 cm^{-1} ;

NMR (CDCl_3 solution): 5.15—4.60 (1H, m), 4.3—3.75 (3H, m), 3.50 (1H, s) and 2.02 (3H, s);

TLC (developing solvent, methylene chloride: methanol=20:1): R_f =0.74.

4.3 g. of 2 - oxa - 6 - *syn* - acetoxy-methyl - 7 - *anti* - hydroxy - *cis* - bicyclo[3,3,0]octan - 3 - one (obtained as described above) were dissolved in 520 ml. of methylene chloride, 25 g. of dihydropyran and 0.52 g. of *p*-toluenesulphonic acid were added and the mixture stirred for 20 minutes at room temperature. The reaction mixture was neutralized with an aqueous solution of sodium bicarbonate, diluted with ethyl acetate, washed with water, dried and concentrated under reduced pressure to give 56 g. of 2 - oxa - 6 - *syn* - acetoxy-methyl - 7 - *anti* - (2 - tetrahydropyranyloxy) - *cis* - bicyclo[3,3,0]octan - 3 - one as a colourless oil having the following physical characteristics:—

IR (liquid film): 2950—2840, 1775, 1740, 1465, 1440, 1390—1340, 1240, 1180, 1140—1120, 1080, 1040 and 980 cm^{-1} ;

NMR (CDCl_3 solution): 5.2—4.72 (1H, m), 4.72—4.30 (1H, m), 4.2—3.2 (5H, m) and 2.01 (3H, s);

TLC (developing solvent, methylene chloride: methanol=20:1): R_f =0.74.

56 g. of the acetyl ether (prepared as described above) were dissolved in 900 ml. of toluene and cooled to -60°C . 456 ml. of a 25 (w/v)% toluene solution of diisobutylaluminium hydride were added and the mixture stirred for 20 minutes at the same temperature; methanol was added in order to decompose the excess of diisobutylaluminium hydride and water was added. The resulting precipitate was filtered off and the filtrate was dried and concentrated under reduced pressure to give 35.2 g. of 2 - oxa - 6 - *syn* - hydroxymethyl - 7 - *anti* - (2 - tetrahydropyranyloxy) - *cis* - bicyclo[3,3,0]octan - 3 - ol as a colourless oil having the following physical characteristics:—

IR (liquid film): 3400, 2940—2860, 1465—1440, 1380, 1355, 1325, 1260, 1200, 1140, 1120, 1075 and 1020 cm^{-1} ;

TLC (developing solvent, ethyl acetate): R_f =0.25.

37.6 g. of sodium hydride (content 63.5%) were suspended in 400 ml. of dimethyl sulphoxide and stirred at 70°C . for 1.5 hours to obtain sodium methylsulphinylmethylide. The reaction mixture was allowed to cool to room temperature and then added dropwise to a solution of 226 g. of (4-carboxybutyl)triphenylphosphonium bromide in 460 ml. of dimethyl sulphoxide, the reaction temperature being kept within the range of 20° to 25°C .

A solution of 35.2 g. of 2 - oxa - 6 - *syn* - hydroxymethyl - 7 - *anti* - (2 - tetrahydropyranyloxy) - *cis* - bicyclo[3,3,0]octan - 3 - ol (prepared as described above) in 90 ml. of dimethyl sulphoxide was added to the above reaction mixture and stirred at 35° to 40°C . for 1.5 hours. The reaction mixture was then poured into 6 litres of ice-water and the neutral substances were removed by extraction with an ethyl acetate-diethyl ether mixture (1:1). The aqueous layer was acidified to pH 2 with saturated aqueous oxalic acid solution and extracted with a diethyl ether-n-pentane mixture

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(1:1). The organic layer was washed with water, dried over sodium sulphate and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel using a benzene-methanol mixture (10:1) as eluent to give 35 g. of 2 α - (6 - carboxyhex - *cis* - 2 - enyl) - 3 β - hydroxymethyl - 4 α - (2 - tetrahydropyranyloxy) - cyclopentan - 1 α - ol as a colourless oil having the following physical characteristics:—

IR (liquid film): 3400, 2940—2860, —2300, 1710, 1450, 1435, 1400, 1355, 1245, 1200, 1140, 1120, 1075 and 1025 cm⁻¹;

NMR (CDCl₃ solution): 6.20 (3H, s), 5.50—5.10 (2H, m), 4.75—4.36 (1H, m), 4.24—3.85 (2H, m), and 3.85—3.0 (4H, m);

TLC (developing solvent, chloroform:tetrahydrofuran:acetic acid=10:2:1): R_f=0.53.

To a solution of 18.8 g. of 2 α - (6 - carboxyhex - *cis* - 2 - enyl) - 3 β - hydroxymethyl - 4 α - (2 - tetrahydropyranyloxy) - cyclopentan - 1 α - ol (obtained as described above) in 130 ml. of diethyl ether, a freshly prepared ethereal solution of diazomethane was added with cooling in an ice-bath until the reaction mixture showed a pale yellow colour. The reaction mixture was concentrated *in vacuo*, and the residue was subjected to column chromatography on silica gel using a cyclohexane-ethyl acetate mixture (2:1) as eluent to give 15.4 g. of 2 α - (6 - methoxycarbonylhex - *cis* - 2 - enyl) - 3 β - hydroxymethyl - 4 α - (2 - tetrahydropyranyloxy) - cyclopentan - 1 α - ol as a colourless oil having the following physical characteristics:—

IR (liquid film): 3450, 2950—2870, 1740, 1440, 1360, 1325, 1250, 1200, 1140, 1120, 1080, and 1025 cm⁻¹;

NMR (CDCl₃ solution): 5.55—5.00 (2H, m), 4.78—4.30 (1H, m), 4.20—3.06 (6H, m), 3.55 (3H, s) and 2.97 (2H, s);

TLC (developing solvent, methylene chloride:methanol=19:1): R_f=0.43.

REFERENCE EXAMPLE 17

2 α -(6-Phenylseleno-6-methoxycarbonylhexyl)-3 β -hydroxymethyl-4 α -(2-tetrahydropyranyloxy)cyclopentan-1 α -ol

Under an atmosphere of nitrogen, a solution of 19.4 ml. of diisopropylamine in 350 ml. of tetrahydrofuran was cooled to -78°C., and to it was added dropwise 114 ml. of a 1.2M solution of *n*-butyllithium in *n*-hexane. The mixture was stirred at -78°C. for 20 minutes to give lithium diisopropylamide. To the lithium diisopropylamide solution was added dropwise a solution of 13.8 g. of 2 α - (6 - methoxycarbonylhexyl) - 3 β - hydroxymethyl - 4 α - (2 - tetrahydropyranyloxy)cyclopentan - 1 α - ol (prepared as described in Reference Example 16) in 100 ml. of tetrahydrofuran at -78°C. and the mixture was stirred at the same temperature for 30 minutes. A solution of 18.2 g. of diphenyl diselenide in 50 ml. of tetrahydrofuran was added dropwise to the reaction mixture at -78°C. and the solution was stirred at the same temperature for one hour and then at 0°C. for 20 minutes. The reaction mixture was poured into an aqueous solution of ammonium chloride and extracted with ethyl acetate. 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 benzene and ethyl acetate (3:2) as eluent to give 15.8 g. of the title compound having the following physical characteristics:

TLC (developing solvent, benzene:ethyl acetate=1:1): R_f=0.37;

IR (liquid film): 3450, 1740, 1580, 1440, 1030 cm⁻¹;

NMR (CDCl₃ solution): 7.75—7.10 (5H, m), 5.00—4.55 (1H, m), 3.70 (3H, s).

REFERENCE EXAMPLE 18

2 α -(6-Methoxycarbonylhex-*trans*-5-enyl)-3 β -hydroxymethyl-4 α -(2-tetrahydropyranyloxy)cyclopentan-1 α -ol

To a solution of 15.8 g. of 2 α - (6 - phenylseleno - 6 - methoxycarbonylhexyl) - 3 β - hydroxymethyl - 4 α - (2 - tetrahydropyranyloxy)cyclopentan - 1 α - ol (prepared as described in Reference Example 17) in a mixture of 200 ml. of ethyl acetate and 100 ml. of tetrahydrofuran were added 4.5 g. of sodium carbonate and 6.2 ml. of 30% hydrogen peroxide and the mixture was stirred at 30°C. for 30 minutes. The reaction mixture was then poured into water, washed with an aqueous solution of sodium carbonate, water and an aqueous solution of sodium chloride, dried over magnesium sulphate and concentrated under reduced pressure to give 10.4 g. of the title compound having the following physical characteristics:

TLC (developing solvent, benzene:ethyl acetate=1:1): R_f=0.28;

IR (liquid film): 3450, 1735, 1660, 1440, 1030 cm⁻¹;

NMR (CDCl₃ solution): 6.90 (1H, dt), 5.82 (1H, d), 5.00—4.55 (1H, m), 3.70 (3H, s).

REFERENCE EXAMPLE 19

1 α -Acetoxy-2 α -(6-methoxycarbonylhex-*trans*-5-enyl)-3 β -hydroxymethyl-4 α -(2-tetrahydropyranyloxy)cyclopentane

Under an atmosphere of nitrogen, a solution of 4.3 ml. of trimethylchlorosilane in 20 ml. of methylene chloride was added dropwise to a solution of 10.4 g. of 2 α -(6-methoxycarbonylhex-*trans*-5-enyl)-3 β -hydroxymethyl-4 α -(2-tetrahydropyranyloxy)cyclopentane - 1 α -ol (prepared as described in Reference Example 18) in a mixture of 150 ml. of methylene chloride and 18.8 ml. of pyridine at -20°C. and the mixture was stirred at the same temperature for 20 minutes. To the solution thus obtained was added dropwise a solution of 2.45 ml. of acetyl chloride in 50 ml. of methylene chloride at -20°C. and the mixture was stirred at room temperature for 30 minutes. Then 3 ml. of ethanol was added to the reaction mixture in order to decompose the excess of acetyl chloride. Pyridine in the solution was quenched with 80 g. of sodium bisulphate, and the resulting precipitate was filtered off. The filtrate was concentrated under reduced pressure. The residue was dissolved in 300 ml. of ethyl acetate, 100 ml. of a saturated aqueous solution of oxalic acid was added and the mixture was stirred vigorously at room temperature for 30 minutes. The reaction mixture was extracted with ethyl acetate, the extract was washed with water, an aqueous solution of sodium bisulphate, 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 benzene and ethyl acetate (3:1) as eluent to give 7.2 g. of the title compound having the following physical characteristics:

TLC (developing solvent, benzene: ethyl acetate=1:1): R_f=0.51;

IR (liquid film): 3450, 1735, 1660, 1440, 1030 cm⁻¹;

NMR (CDCl₃ solution): 6.90 (1H, dt), 5.82 (1H, d), 5.25—4.90 (1H, m), 4.85—4.45 (1H, m), 3.71 (3H, s), 2.05 (3H, s).

REFERENCE EXAMPLE 20

1 α -Acetoxy-2 α -(6-methoxycarbonylhex-*trans*-5-enyl)-3 β -formyl-4 α -(2-tetrahydropyranyloxy)cyclopentane

Under an atmosphere of nitrogen, 34 ml. of pyridine were dissolved in 440 ml. of methylene chloride, 20.2 g. of chromium trioxide were added with stirring and the mixture was stirred at room temperature for 15 minutes. 88 g. of infusorial earth were added to the reaction mixture and the solution was cooled to 0°C. A solution of 7.2 g. of 1 α -acetoxy-2 α -(6-methoxycarbonylhex-*trans*-5-enyl)-3 β -hydroxymethyl-4 α -(2-tetrahydropyranyloxy)cyclopentane (prepared as described in Reference Example 19) in 100 ml. of methylene chloride at 0°C. was added. After 10 minutes stirring at 0°C., 155 g. of sodium bisulphate were added to the reaction mixture and stirring was continued for a further 10 minutes. The resulting precipitate was filtered through a pad of magnesium sulphate and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of benzene and ethyl acetate (5:1) as eluent to give 5.85 g. of the title compound having the following physical characteristics:

TLC (developing solvent, benzene: ethyl acetate=2:1): R_f=0.67;

IR (liquid film): 1735, 1660, 1440, 1250, 1030 cm⁻¹;

NMR (CDCl₃ solution): 10.00—9.70 (1H, m), 6.90 (1H, dt), 5.82 (1H, d), 5.30—4.96 (1H, m), 4.75—4.10 (2H, m), 3.72 (3H, s), 2.06 (3H, s).

REFERENCE EXAMPLE 21

Methyl 9 α -acetoxy-11 α -(2-tetrahydropyranyloxy)-15-oxo-16,16-dimethylprosta-*trans*-2,*trans*-13-dienoate

Under an atmosphere of nitrogen, a solution of 1.62 g. of dimethyl 2-oxo-3,3-dimethylheptylphosphonate (prepared as described in British Patent Specification No. 1398291) in 6 ml. of tetrahydrofuran was added to a suspension of 230 mg. of sodium hydride (63% content) in 50 ml. of tetrahydrofuran and the mixture was stirred at room temperature for 30 minutes. To the solution thus obtained was added a solution of 1.98 g. of 1 α -acetoxy-2 α -(6-methoxycarbonylhex-*trans*-5-enyl)-3 β -formyl-4 α -(2-tetrahydropyranyloxy)cyclopentane (prepared as described in Reference Example 20) in 10 ml. of tetrahydrofuran at room temperature and the solution was stirred at the same temperature for one hour. The reaction mixture was quenched with acetic acid, filtered through a pad of silica gel and the filtrate was concentrated under reduced pressure. The residue was purified by column chromato-

graphy on silica gel using a mixture of benzene and ethyl acetate (8:1) as eluent to give 2.36 g. of the title compound having the following physical characteristics:

TLC (developing solvent, benzene: ethyl acetate=2:1): R_f =0.71;

IR (liquid film): 1730, 1660, 1630, 1440, 1030 cm^{-1} ;

NMR (CDCl_3 solution): 7.20—6.50 (2H, m), 6.16 (1H, d), 5.80 (1H, d), 5.30—4.90 (1H, m), 4.80—4.50 (1H, m), 3.72 (3H, s), 2.06 (3H, s), 1.10—0.70 (9H, m).

REFERENCE EXAMPLE 22

Methyl 9 α -acetoxy-11 α -(2-tetrahydropyranyloxy)-15 α -hydroxy-16,16-dimethylprosta-*trans*-2,*trans*-13-dienoate

To a solution of 2.36 g. of methyl 9 α -acetoxy-11 α -(2-tetrahydropyranyloxy)-15-oxo-16,16-dimethylprosta-*trans*-2,*trans*-13-dienoate (prepared as described in Reference Example 21) in 40 ml. of methanol was added 700 mg. of sodium borohydride at -40°C . and the solution was stirred at that temperature for 20 minutes. The reaction mixture was quenched with acetic acid and concentrated under reduced pressure. The residue was dissolved in ethyl acetate and the solution 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. The residue was purified by column chromatography on silica gel using a mixture of benzene and ethyl acetate (4:1) as eluent to give 790 mg. of the title compound, 810 mg. of its 15 β -hydroxy isomer and 480 mg. of a mixture of the isomers. The title compound showed the following physical characteristics:

TLC (developing solvent, benzene: ethyl acetate=2:1): R_f =0.38, (15 β -hydroxy isomer, R_f =0.47);

IR (liquid film): 3450, 1730, 1660, 1440, 1030, 980 cm^{-1} ;

NMR (CDCl_3 solution): 7.20—6.70 (1H, m), 6.10—4.90 (4H, m), 4.80—4.50 (1H, m), 3.72 (3H, s), 2.06 (3H, s), 1.10—0.70 (9H, m).

REFERENCE EXAMPLE 23

Methyl 9 α -acetoxy-11 α ,15 α -bis(2-tetrahydropyranyloxy)-16,16-dimethylprosta-*trans*-2,*trans*-13-dienoate

To a solution of 790 mg. of methyl 9 α -acetoxy-11 α -(2-tetrahydropyranyloxy)-15 α -hydroxy-16,16-dimethylprosta-*trans*-2,*trans*-13-dienoate (prepared as described in Reference Example 22) in 15 ml. of methylene chloride were added 5 mg. of *p*-toluenesulphonic acid and 0.3 ml. of 2,3-dihydropyran and the mixture was stirred at room temperature for 20 minutes. The reaction mixture was diluted with 50 ml. of ethyl acetate, washed with an aqueous solution of sodium chloride, dried over magnesium sulphate and concentrated under reduced pressure to give 930 mg. of the crude title compound having the following physical characteristics:

TLC (developing solvent, benzene: ethyl acetate=2:1): R_f =0.67;

IR (liquid film): 1730, 1660, 1440, 1030, 980 cm^{-1} ;

NMR (CDCl_3 solution): 7.20—6.70 (1H, m), 6.10—4.90 (4H, m), 4.80—4.50 (2H, m), 3.72 (3H, s), 2.06 (3H, s), 1.10—0.70 (9H, m).

REFERENCE EXAMPLE 24

Methyl 9 α -hydroxy-11 α ,15 α -bis(2-tetrahydropyranyloxy)-16,16-dimethylprosta-*trans*-2,*trans*-13-dienoate

To a solution of 930 mg. of methyl 9 α -acetoxy-11 α ,15 α -bis(2-tetrahydropyranyloxy)-16,16-dimethylprosta-*trans*-2,*trans*-13-dienoate (prepared as described in Reference Example 23) in 12 ml. of methanol was added 400 mg. of potassium carbonate and the mixture was stirred at 40°C . for 1.5 hours. The reaction mixture was quenched with acetic acid and extracted with ethyl acetate. The extract was washed with an aqueous solution of sodium bicarbonate, 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 benzene and ethyl acetate (6:1) as eluent to give 745 mg. of the title compound having the following physical characteristics:

TLC (developing solvent, benzene: ethyl acetate=2:1): R_f =0.47;

IR (liquid film): 3450, 2930, 2850, 1725, 1660, 1440, 1140 1080 and 980 cm^{-1} ;

NMR (CDCl_3 solution): 7.20—6.70 (1H, m), 6.10—5.30 (3H, m), 4.80—4.50 (2H, m), 3.72 (3H, s), 1.10—0.70 (9H, m).

EXAMPLE 8

Methyl 9-oxo-11 α ,15 α -dihydroxy-16,16-dimethylprosta-*trans*-2,*trans*-13-dienoate
[or 16,16-dimethyl-*trans*-2,3-didehydro-PGE₁ methyl ester]

To a solution of 745 mg. of methyl 9 α -hydroxy-11 α ,15 α -bis-(2-tetrahydropyranyloxy)-16,16-dimethylprosta-*trans*-2,*trans*-13-dienoate (prepared as described in Reference Example 24) in 22 ml. of diethyl ether was added a chromic acid solution (obtained from 0.94 g. of chromium trioxide, 4.55 g. of manganese sulphate and 1.06 ml. of sulphuric acid in 22 ml. of water), and the mixture was stirred at 0°C. for one hour. The reaction mixture was then extracted with diethyl ether and the extract was washed with an aqueous solution of sodium chloride, dried over magnesium sulphate and concentrated under reduced pressure to give 732 mg. of methyl 9-oxo-11 α ,15 α -bis-(2-tetrahydropyranyloxy)-16,16-dimethylprosta-*trans*-2,*trans*-13-dienoate having the following physical characteristic:

TLC (developing solvent, benzene:ethyl acetate=2:1): Rf=0.74.

To a solution of 732 mg. of the 9-oxo-compound (prepared as described above) in 1.9 ml. of tetrahydrofuran was added 19 ml. of a 65% (v/v) aqueous solution of acetic acid and the solution was stirred at 55° to 60°C. for one hour. The reaction mixture was then extracted with ethyl acetate and the extract was washed with water and an aqueous solution of sodium chloride, dried over magnesium sulphate and concentrated under reduced pressure to give 119 mg. of the title compound having the same physical characteristics as the product of Examples 3 and 7.

REFERENCE EXAMPLE 25

Methyl 9 α -acetoxy-11 α -(2-tetrahydropyranyloxy)-15-oxo-17(ξ),20-diethylprosta-*trans*-2,*trans*-13-dienoate

By proceeding as described in Reference Example 21, but replacing the dimethyl 2-oxo-3,3-dimethylheptylphosphonate by 1.62 g. of dimethyl 2-oxo-4(ξ)-ethylonylphosphonate (prepared as described in Reference Example 3), there were obtained 2.3 g. of the title compound having the following physical characteristics:

TLC (developing solvent, benzene:ethyl acetate=2:1): Rf=0.70;

IR (liquid film): 1730, 1660, 1630, 1440, 1030 cm⁻¹;

NMR (CDCl₃ solution): 7.20—6.50 (2H, m), 6.16 (1H, d), 5.80 (1H, d), 5.35—4.90 (1H, m), 4.85—4.50 (1H, m), 3.72 (3H, s), 2.06 (3H, s), 1.10—0.70 (6H, m).

REFERENCE EXAMPLE 26

Methyl 9 α -acetoxy-11 α -(2-tetrahydropyranyloxy)-15 α -hydroxy-17(ξ),20-diethylprosta-*trans*-2,*trans*-13-dienoate

By proceeding as described in Reference Example 22 but replacing the methyl 9 α -acetoxy-11 α -(2-tetrahydropyranyloxy)-15-oxo-16,16-dimethylprosta-*trans*-2,*trans*-13-dienoate by 2.3 g. of methyl 9 α -acetoxy-11 α -(2-tetrahydropyranyloxy)-15-oxo-17(ξ),20-diethylprosta-*trans*-2,*trans*-13-dienoate (prepared as described in Reference Example 25) there were obtained 720 mg. of the title compound, 740 mg. of its 15 β -hydroxy isomer and 500 mg. of a mixture of the isomers. The title compound showed the following physical characteristics:

TLC (developing solvent, benzene:ethyl acetate=2:1): Rf=0.40, (15 β -hydroxy isomer, Rf=0.47);

IR (liquid film): 3450, 1730, 1660, 1440, 1030, 980 cm⁻¹;

NMR (CDCl₃ solution): 7.20—6.70 (1H, m), 6.10—4.90 (4H, m), 4.80—4.50 (1H, m), 3.72 (3H, s), 2.06 (3H, s), 1.10—0.70 (6H, m).

REFERENCE EXAMPLE 27

Methyl 9 α -acetoxy-11 α ,15 α -bis-(2-tetrahydropyranyloxy)-17(ξ),20-diethylprosta-*trans*-2,*trans*-13-dienoate

By proceeding as described in Reference Example 23 but replacing the methyl 9 α -acetoxy-11 α -(2-tetrahydropyranyloxy)-15 α -hydroxy-16,16-dimethylprosta-*trans*-2,*trans*-13-dienoate by 720 mg. of methyl 9 α -acetoxy-11 α -(2-tetrahydropyranyloxy)-15 α -hydroxy-17(ξ),20-diethylprosta-*trans*-2,*trans*-13-dienoate (prepared as described in Reference Example 26) dissolved in 13 ml. of methylene chloride and utilizing 5 mg. of *p*-toluenesulphonic acid and 0.3 ml. of 2,3-dihydropyran there were obtained 870 mg. of the title compound having the following physical characteristics:

TLC (developing solvent, benzene:ethyl acetate=2:1): Rf=0.64;
IR (liquid film): 1730, 1660, 1440, 1030, 980 cm^{-1} ;
NMR (CDCl_3 solution): 7.20—6.70 (1H, m), 6.10—4.90 (4H, m), 4.80—4.50 (2H, m), 3.72 (3H, s), 2.06 (3H, s), 1.10—0.70 (6H, m).

REFERENCE EXAMPLE 28

Methyl 9 α - hydroxy - 11 α ,15 α - bis - (2 - tetrahydropyranyloxy) - 17(ξ),20 - diethylprosta - *trans* - 2,*trans* - 13 - dienoate

By proceeding as described in Reference Example 24 but replacing the methyl 9 α - acetoxy - 11 α ,15 α - bis - (2 - tetrahydropyranyloxy) - 16,16 - dimethylprosta - *trans* - 2,*trans* - 13 - dienoate by 870 mg. of methyl 9 α - acetoxy - 11 α ,15 α - bis - (2 - tetrahydropyranyloxy) - 17(ξ),20 - diethylprosta - *trans* - 2,*trans* - 13 - dienoate (prepared as described in Reference Example 27) dissolved in 11 ml. of methanol and utilizing 380 mg. of potassium carbonate there were obtained 700 mg. of the title compound having the following physical characteristics:

TLC (developing solvent, benzene:ethyl acetate=2:1): Rf=0.50;
IR (liquid film): 3440, 2930, 2850, 1730, 1655, 1435, 1140, 1085, 1030 and 985 cm^{-1} ;
NMR (CDCl_3 solution): 6.95 (1H, dt), 5.79 (1H, d), 5.80—5.15 (2H, m), 4.90—4.50 (2H, m), 3.71 (3H, s).

EXAMPLE 29

Methyl 9-oxo-11 α ,15 α -dihydroxy-17(ξ),20-diethylprosta-*trans*-2,*trans*-13-dienoate [or 17(ξ),20-diethyl-*trans*-2,3-didehydro-PGE₁ methyl ester]

By proceeding as described in Example 8 but replacing the methyl 9 α - hydroxy - 11 α ,15 α - bis - (2 - tetrahydropyranyloxy) - 16,16 - dimethylprosta - *trans* - 2,*trans* - 13 - dienoate by 700 mg. of methyl 9 α - hydroxy - 11 α ,15 α - bis - (2 - tetrahydropyranyloxy) - 17(ξ),20 - diethylprosta - *trans* - 2,*trans* - 13 - dienoate (prepared as described in Reference Example 28) dissolved in 21 ml. of diethyl ether and utilizing 21 ml. of a chromic acid solution (prepared as described in Example 8) there was obtained methyl 9 - oxo - 11 α ,15 α - bis - (2 - tetrahydropyranyloxy) - 17(ξ),20 - diethylprosta - *trans* - 2,*trans* - 13 - dienoate having the following physical characteristics:

TLC (developing solvent, benzene:ethyl acetate=2:1): Rf=0.68.

Proceeding as described in Example 8 the 9-oxo compound (prepared as described above) was then dissolved in 1.8 ml. of tetrahydrofuran and utilizing 18 ml. of 65% (v/v) aqueous acetic acid there were obtained 99 mg. of the title compound having the same physical characteristics as the product of Example 4.

The present invention includes within its scope pharmaceutical compositions which comprise, as active ingredient, at least one prostaglandin analogue of general formula VI or methyl ester thereof, or a cyclodextrin clathrate of such prostaglandin analogue or ester thereof, or a non-toxic salt of such a prostaglandin analogue, together with a pharmaceutical carrier or coating. In clinical practice the new compounds of the present invention will normally be administered orally, vaginally, rectally or parenterally.

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, mannitol, or lactose. 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 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 include capsules or absorbable material such as gelatin containing one or more of the active substances with or without the addition of diluents or excipients.

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

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

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. The 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.

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 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.

In the human adult, the doses per person are generally between 0.01 and 1 mg. by oral administration in the treatment of hypertension, between 1—1000 μ g. by oral, intravaginal, intravenous or extra-amniotic administration for contraception and the menstrual regulation in females and in the termination of pregnancy and the induction of labour in pregnant females.

In domestic female mammals such as cows, mares, sows, ewes and bitches, the doses are generally between 0.001 and 50 mg./animal by intramuscular, subcutaneous, intrauterine, intravaginal and intravenous administration for the synchronisation of oestrus, treatment of impaired fertility and the induction of abortion and of labour.

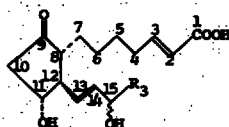
The following Example illustrates pharmaceutical compositions according to the invention.

EXAMPLE 10

16,16-Dimethyl-*trans*-2,3-didehydro-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 (micro-fine 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 16,16-dimethyl-*trans*-2,3-didehydro-PGE₁ methyl ester which after swallowing of the capsule is released into the stomach. "Aerosil" is a registered Trade Mark.

WHAT WE CLAIM IS:—

1. Prostaglandin analogues of the general formula:—



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(wherein R₃ represents the 1,1-dimethylpentyl or 2(ξ)-ethylheptyl group, the wavy line indicates attachment of the hydroxy group in beta or alpha configuration and the C₂—C₃ and C₁₃—C₁₄ double bonds are *trans*) and methyl esters thereof, and cyclodextrin clathrates of such acids or esters, and non-toxic salts of such acids.

2. Prostaglandin compounds according to claim 1 in which the hydroxy group attached to the 15-position carbon atom is in alpha configuration.

3. 16,16-Dimethyl-*trans*-2,3-didehydro-PGE₁ and non-toxic salts thereof.

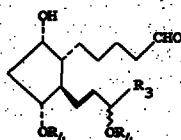
4. 17(ξ),20-Diethyl-*trans*-2,3-didehydro-PGE₁ and non-toxic salts thereof.

5. 16,16-Dimethyl-*trans*-2,3-didehydro-PGE₁ methyl ester.

6. 17(ξ),20-Diethyl-*trans*-2,3-didehydro-PGE₁ methyl ester.

7. Cyclodextrin clathrates of a prostaglandin analogue or methyl ester thereof claimed in any one of claims 3 to 6.

8. Process for the preparation of prostaglandin analogues of the general formula depicted in claim 1 and methyl esters thereof, which comprises reacting a cyclopentane derivative of the general formula:—



VII



vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. The 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.

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 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.

In the human adult, the doses per person are generally between 0.01 and 1 mg. by oral administration in the treatment of hypertension, between 1—1000 μ g. by oral, intravaginal, intravenous or extra-amniotic administration for contraception and the menstrual regulation in females and in the termination of pregnancy and the induction of labour in pregnant females.

In domestic female mammals such as cows, mares, sows, ewes and bitches, the doses are generally between 0.001 and 50 mg./animal by intramuscular, subcutaneous, intrauterine, intravaginal and intravenous administration for the synchronisation of oestrus, treatment of impaired fertility and the induction of abortion and of labour.

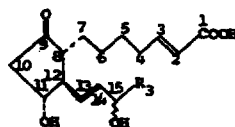
The following Example illustrates pharmaceutical compositions according to the invention.

EXAMPLE 10

16,16-Dimethyl-*trans*-2,3-didehydro-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 (micro-fine 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 16,16-dimethyl-*trans*-2,3-didehydro-PGE₁ methyl ester which after swallowing of the capsule is released into the stomach. "Aerosil" is a registered Trade Mark.

WHAT WE CLAIM IS:—

1. Prostaglandin analogues of the general formula:—



VI

(wherein R₃ represents the 1,1-dimethylpentyl or 2(ξ)-ethylheptyl group, the wavy line indicates attachment of the hydroxy group in beta or alpha configuration and the C₂—C₃ and C₁₃—C₁₄ double bonds are *trans*) and methyl esters thereof, and cyclodextrin clathrates of such acids or esters, and non-toxic salts of such acids.

2. Prostaglandin compounds according to claim 1 in which the hydroxy group attached to the 15-position carbon atom is in alpha configuration.

3. 16,16-Dimethyl-*trans*-2,3-didehydro-PGE₁ and non-toxic salts thereof.

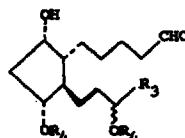
4. 17(ξ),20-Diethyl-*trans*-2,3-didehydro-PGE₁ and non-toxic salts thereof.

5. 16,16-Dimethyl-*trans*-2,3-didehydro-PGE₁ methyl ester.

6. 17(ξ),20-Diethyl-*trans*-2,3-didehydro-PGE₁ methyl ester.

7. Cyclodextrin clathrates of a prostaglandin analogue or methyl ester thereof claimed in any one of claims 3 to 6.

8. Process for the preparation of prostaglandin analogues of the general formula depicted in claim 1 and methyl esters thereof, which comprises reacting a cyclopentane derivative of the general formula:—

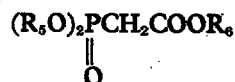


VII



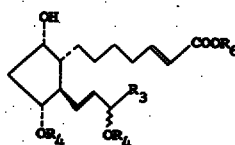
41

(wherein R_4 represents a 2-tetrahydropyranyl group unsubstituted or substituted by at least one alkyl radical or a 1-ethoxyethyl group, R_3 is as defined in claim 1, the wavy line indicates attachment of the OR_4 group to the carbon atom in alpha or beta configuration, and the depicted double bond is *trans*) with a dialkyl phosphonate of the general formula:—



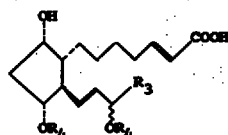
VIII

(wherein R_5 represents a methyl or ethyl radical, and R_6 represents the methyl radical or a straight- or branched-chain alkyl radical containing from 2 to 12 carbon atoms), optionally hydrolysing when R_6 is the methyl radical, or hydrolysing when R_6 is an alkyl radical containing from 2 to 12 carbon atoms, the resulting prostaglandin ester of the general formula:—



IX

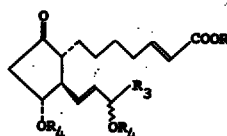
(wherein R_3 , R_4 , R_6 and the wavy line have the meanings hereinbefore specified and the depicted double bonds are *trans*) to the corresponding acid of the general formula:—



X

(wherein R_3 , R_4 and the wavy line have the meanings hereinbefore specified, and the depicted

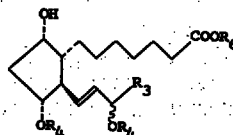
double bonds are *trans*), converting by methods known *per se*, the 9 α -hydroxy group in the compound of general formula IX (wherein R_6 represents the methyl radical) or X to an oxo group, and hydrolyzing the OR_4 groups in the resulting prostaglandin compound of the general formula:—



XI

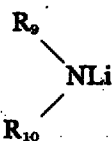
(wherein R represents a hydrogen atom or the methyl radical, and R_3 , R_4 and the wavy line have the meanings hereinbefore specified, and the depicted double bonds are *trans*) to hydroxy groups to obtain a PGE compound of the general formula depicted in claim 1 or a methyl ester thereof.

9. Process for the preparation of prostaglandin analogues of the general formula depicted in claim 1 and methyl esters thereof, which comprises reacting a compound of the general formula:—



XVI

(wherein the various symbols and the wavy line are as defined in claim 8 and the depicted double bond is *trans*) with a compound of the general formula:—



XVII

(wherein R_9 and R_{10} , which may be the same or different, each represents a straight-

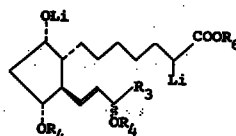


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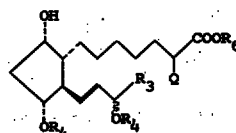
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or branched-chain alkyl group containing from 1 to 6 carbon atoms or a cycloalkyl group containing from 3 to 6 carbon atoms) to obtain a lithium ester enolate of the general formula:—



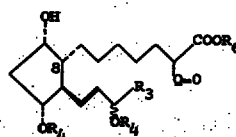
XVIII

(wherein the various symbols and $\sim$ are as defined in claim 8 and the double bond is *trans*), reacting the lithium ester enolate with benzeneselenenyl bromide or diphenyl diselenide or a dialkyl or diphenyldisulphide of the formula $R_{11}SSR_{11}$, wherein the symbols R_{11} both represent alkyl groups containing from 1 to 4 carbon atoms or phenyl radicals, hydrolysing the resulting intermediate to convert the $-OLi$ group attached to the cyclopentane ring to an α -hydroxy group and to obtain a compound of the general formula:—



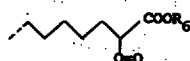
XIX

(wherein R_3 , R_4 , R_6 and $\sim$ are as defined in claim 8, Q represents $-Se\phi$, in which ϕ represents the phenyl radical, or a group $-SR_{11}$, in which R_{11} is as hereinbefore defined, and the depicted double bond is *trans*) treating the resulting compound with hydrogen peroxide or sodium periodate, and decomposing the resulting compound of the general formula:—



XX

(wherein the various symbols and $\sim$ are as defined in claim 8, and the depicted double bond is *trans*) to convert the grouping

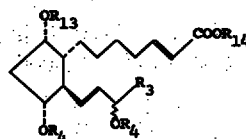


attached to the 8-position of the cyclopentane ring to a *trans*- Δ^2 -grouping



wherein R_6 is as defined in claim 8 and the depicted double bond is *trans*, to obtain a compound of general formula IX specified in claim 8, and treating the compound of formula IX as specified in claim 8 to obtain a PGE compound of the general formula depicted in claim 1 or a methyl ester thereof.

10. Process for the preparation of prostaglandin analogues of the general formula depicted in claim 1 and methyl esters thereof, which comprises the hydrolysis under alkaline conditions of a compound of the general formula:—

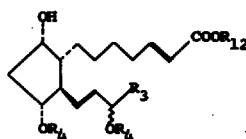


XXIV

(wherein R_3 , R_4 and $\sim$ are as defined in claim 8, R_{13} represents an alkanoyl group containing from 2 to 5 carbon atoms and R_{14} represents a straight- or branched-chain alkyl radical containing from 1 to 4 carbon atoms and the depicted double bonds are *trans*) to obtain a compound of the general formula:—



(43)



XXIII

(wherein R_3 , R_4 and $\sim$ are as defined in claim 8, R_{12} represents a hydrogen atom, the methyl radical or a straight- or branched-chain alkyl radical containing from 2 to 4 carbon atoms and the depicted double bonds are *trans*) and treating the compound of general formula XXIII as specified in claim 8 for the treatment of a compound of formula IX or X to obtain a PGE compound of the general formula depicted in claim 1 or a methyl-ester thereof.

11. Process according to claim 10 in which the hydrolysis under alkaline conditions is effected with an aqueous solution of an alkali metal hydroxide or carbonate in the presence of a water miscible organic solvent or with anhydrous potassium carbonate in an anhydrous alkanol containing from 1 to 4 carbon atoms.

12. Process according to claim 11 in which the alkali metal hydroxide or carbonate is sodium or potassium hydroxide or carbonate.

13. Process according to claim 11 or 12 in which the water miscible organic solvent is tetrahydrofuran or an alkanol containing from 1 to 4 carbon atoms.

14. Process according to claim 10 in which the alkaline hydrolysis is effected with potassium carbonate in absolute methanol.

15. Process according to any one of claims 8 to 14 followed by the step of converting by methods known *per se* a prostaglandin acid product of the general formula depicted in claim 1 into a methyl ester or into a non-toxic salt.

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 the general formula depicted in claim 1, or a methyl ester thereof, into a cyclodextrin clathrate.

17. Process for the preparation analogues of the general formula depicted in claim 1 or methyl esters or non-toxic salts thereof substantially as hereinbefore described with especial reference to Examples 1 to 4.

18. Process for the preparation of prostaglandin analogues of the general formula depicted in claim 1 or methyl esters or non-toxic salts thereof substantially as hereinbefore described with especial reference to Examples 5 to 7.

19. Process for the preparation of prostaglandin analogues of the general formula depicted in claim 1 or methyl esters or non-toxic salts thereof substantially as hereinbefore described with especial reference to Example 8 and 9.

20. Prostaglandin analogues of the general formula depicted in claim 1 and methyl esters and non-toxic salts thereof, and cyclodextrin clathrates of said prostaglandin analogues and esters thereof, when prepared by the process claimed in any one of claims 8 to 19.

21. Pharmaceutical compositions which comprise, as active ingredient, at least one prostaglandin analogue as claimed in claim 1, 2, 3 or 4 or a methyl ester thereof, or a cyclodextrin clathrate of such a prostaglandin analogue or methyl ester thereof, or a non-toxic salt of such a prostaglandin analogue, in association with a pharmaceutical carrier.

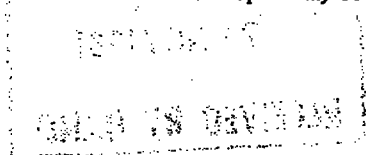
22. Pharmaceutical compositions according to claim 21 in which the active ingredient is 16,16-dimethyl-*trans*-2,3-didehydro-PGE₁ methyl ester or 17(ξ),20-diethyl-*trans*-2,3-didehydro-PGE₁ methyl ester.

23. Pharmaceutical compositions according to claim 21 substantially as hereinbefore described.

24. Pharmaceutical compositions according to claim 21 substantially as hereinbefore described in Example 10.

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Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1979
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from
which copies may be obtained.



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