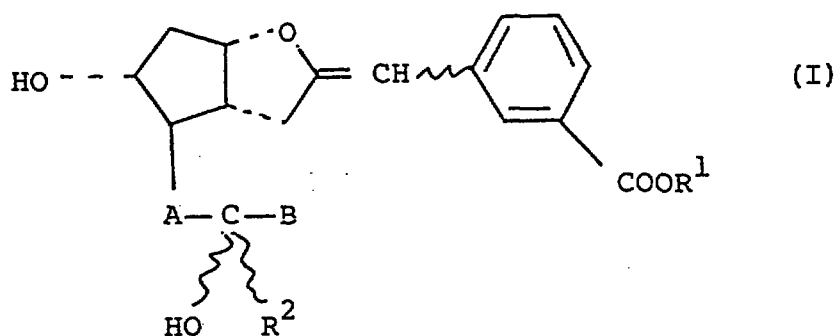


Heterocyclic compounds, medicaments containing them and processes for preparing these heterocyclic compounds and medicaments

The present invention relates to heterocyclic compounds of the formula



the basic structure of which for example is also contained
5 in the naturally occurring prostacyclin.

R¹ represents a hydrogen atom, a pharmaceutically acceptable cation or a linear or branched C₁-C₆ alkyl radical. Preferably R¹ represents, however, a methyl or an ethyl radical or, in the case when
10 the group R¹ represents a cation, a sodium or a potassium ion. Other suitable cations are known from their use in the chemistry of prostaglandins or prostacyclin, respectively. For instance there may be used the ions of calcium, magnesium, ammonium or of amines such as mono-, di- or trimethyl-
15 amine, -ethylamine, -ethanolamine, tris-hydroxymethylamine and others. Furthermore for the salt formation also basic amino acids like arginine or lysine may be used.

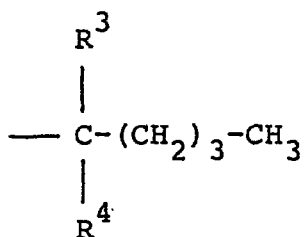
R² represents hydrogen or a methyl radical. At

- 3 -

the carbon atom (15) bearing the group R^2 (and others) there may exist the RS- or S-configuration. In the compounds of formula I the 15S forms of the compounds of formula I are preferred.

5 A is a group selected from $-CH_2-CH_2-$, (trans)-CH=CH- and $-C\equiv C-$. The two last mentioned radicals are preferred and especially in the preferred 15S-forms of the compounds of formula I A is preferably (trans)-CH=CH-.

10 B either represents a $C_5 - C_9$ alkyl radical and having the structure

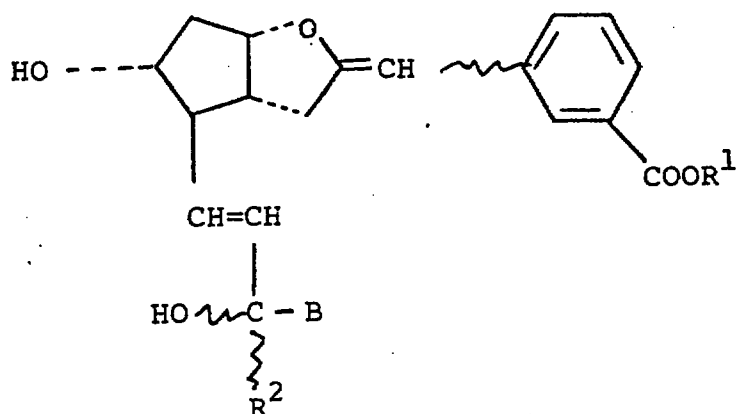


wherein R^3 and R^4 have the same or a different meaning and each represents hydrogen, methyl or ethyl or B represents a cyclohexyl radical which may be substituted 15 in position 4' by a methyl or an ethyl radical.

In preferred groups, B represents the cyclohexyl radical or the alkyl radical of the structure given above wherein both of R^3 and R^4 are hydrogen or methyl or wherein R^3 is hydrogen and R^4 is ethyl 20 respectively.

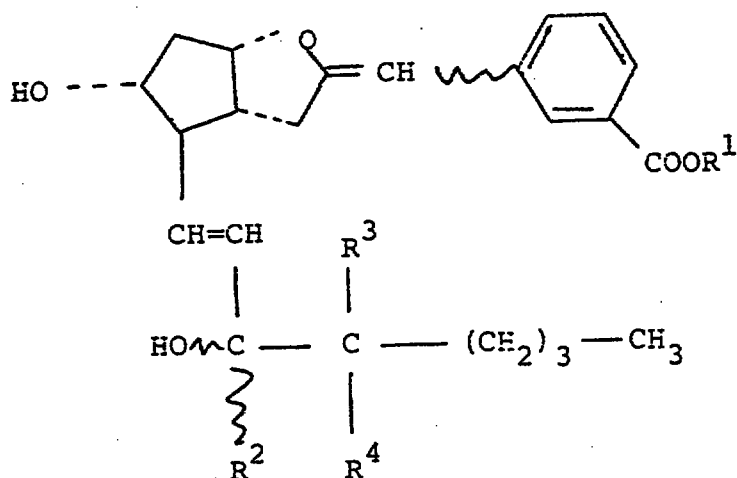
In formula I the phenyl radical may be arranged with respect to the double bond in the E-, EZ- or preferably in the Z-configuration.

25 If A is as preferred the (trans)-CH=CH-radical the compounds according to the invention correspond to the formula

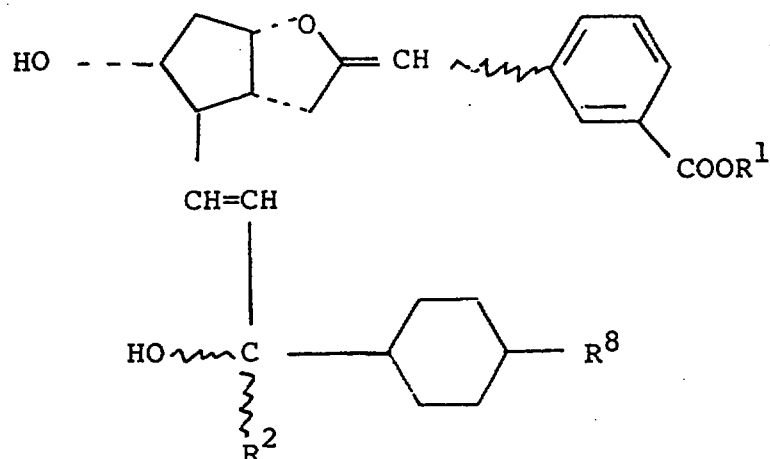


wherein R¹, R² and B have the same meaning as in formula I. Accordingly the especially preferred compounds

- 5 in which A is the (trans)-CH=CH- group and in which B is the alkyl or cycloalkyl radical mentioned above have the following structures.



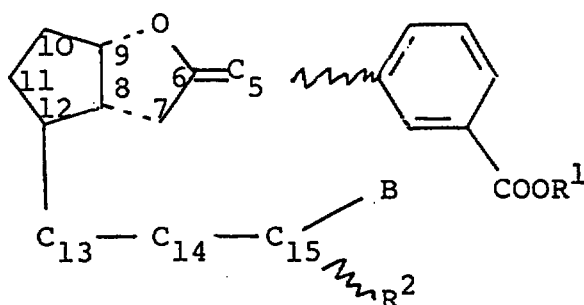
wherein R¹ to R⁴ have the same meaning as above, and



wherein R^1 and R^2 are as defined above and wherein R^8 represents hydrogen, methyl or ethyl.

With respect to the nomenclature of the compounds of formula I reference is made to the papers of Nelson, J. Med. Chem. 17, 911 (1974), and Johnson *et al.*, Prostaglandins 15, 737 (1978). Accordingly the carbon atoms in the basic structure of the compounds of formula I are numbered as follows:

10



wherein in consideration of the definition given above for A the carbon atoms 13 and 14 may also be connected by a double or triple bond and wherein R^1 , R^2 and B have the same meaning as in formula I. The numbering of the carbon atoms in these radicals needs no special explanation besides mentioning that in case B is a cyclohexyl radical the carbon atoms thereof will become numbered as 1', 2' etc. (as may be seen also from the

definition given for B hereinabove).

Many derivatives of prostacyclin are known, for example, from EP-A 9869 and DE-A 27 02 553, which can also contain phenyl radicals in their molecule among other things. However, these are either linked with the carboxyl group of the prostacyclin in ester fashion in the form of optionally substituted phenol radicals or the phenyl or aryl radicals are bound on one of the carbon atoms 15 or 16 etc. of the prostacyclin. DE-A 27 02 553 also relates to derivatives of prostacyclin in which the carboxyl group is completely replaced by a tetrazolyl-5-radical or, for example, by a dialkyl aminomethyl group. As it is known that the replacement of a carboxyl group by a tetrazolyl radical in a pharmacologically effective substance leads to an at least qualitatively equivalent product and as it is also known that the replacement of the carboxyl group in prostaglandins by a dimethylamino group leads to prostaglandin antagonists (J. Pharmacol. Exp. Ther. 206 (1978) 139) it was impossible to make predictions based on the prior art as to how the first replacement of the aliphatic chain of carbon atoms 2, 3, and 4 in the prostacyclin molecule by a phenylene ring would turn out pharmacologically and with respect to accessibility and stability of the resulting products.

Therefore it is surprising that not

only the compounds of formula I have prostacyclin-like properties with respect to blood platelet aggregation (in-vitro and in-vivo) and with respect to the blood pressure but also that they are distinguished however from prostacyclin for instance in that they are far more stable than prostacyclin. Compared with 5,6-dihydroprostacyclin, which is considered as a reference compound due to its chemical stability, e.g. the product obtained in example 3b herein is several times more active. For the compounds according to the invention the relation of their blood platelet aggregation inhibiting effect to their blood pressure lowering activity is surprising: Contrary to 5,6-dihydroprostacyclin which produces both these effects at the same dosage range the compounds of formula I produce blood pressure lowering effects only after administering far higher dosages than those necessary to produce platelet aggregation inhibition as may be seen from the following tables 1a - 1d in which for some compounds of formula I the experimentally (in the in-vivo-experiments each time using groups of 4 to 6 animals) obtained values of the relative activity in comparison to 5,6-dihydroprostacyclin are given:

25 Table 1a

Relative activity against the aggregation of human thrombocytes induced by arachidonic acid in-vitro (the IC_{50} , i.e. the concentration causing under the experimental conditions in 50% of the cases inhibition of the platelet aggregation, for 5,6-dihydroprostacyclin is $0.18 \mu \text{ Mol/l}$):

5	Test compound	5,6-Di-hydro-prosta-cyclin	1e)ii)	Product of example No.				
				1e)i)	2a	2b	3b	4b
	rela-tive acti-vity	1.0	0.25	0.86	1.2	1.2	18.0	0.31

10 Table 1b

Relative activity on the ADP induced fall in platelet count in vivo in narcotized rats (urethane narcosis; intravenous administration of the test compounds; the ED₅₀ for 5,6-dihydroprostacyclin under these
15 experimental conditions is 0.0114 mg/kg):

Test compound	5,6-Dihydro-prostacyclin	Product of example No			
		ie)ii)	le)i)	3b	4b
20					
relative activity	1.0	0.97	1.3	5.0	0.2

It is remarkable that especially the product of example 3b is several times more active than 5,6-dihydroprostacyclin in-vitro (table 1a) as well as in-vivo (table 1b).

25 Table 1c

Relative blood pressure lowering activity in

conscious, spontaneous hypertensive rats (measurement via in-dwelling catheter; intravenous administration of the test compounds; the ED₂₀ for 5,6-dihydroprostacyclin under these experimental conditions is 0.005 mg/kg):

Test compound	5,6-Dihydroprostacyclin	Product of example No.			
		1e)ii)	1e)i)	3b	4b
relative activity	1.0	0.014	0.1	0.25	0.012

Table 1d

Index of selectivity ($\frac{\text{aggregation inhibiting activity}}{\text{blood pressure lowering activity}}$) in comparison to 5,6-dihydroprostacyclin (calculated from the values given in tables 1b and 1c)

Test compound	5,6-Dihydroprostacyclin	Product of example No.			
		1e)ii)	1e)i)	3b	4b
Index of selectivity	1.0	69.3	13.0	20.0	16.7

These results prove that the compounds of formula I can be used not only in diseases in which an inhibition of platelet aggregation is desired without

(18)

accompanying lowering of the blood pressure (as for instance hyperaggregability in coronary heart disease) but also in higher doses in diseases in which a simultaneous vasodilation is desired (as for instance

5 ischaemic peripheral vascular disease).

Natural prostacyclin and also the chemically stable 5,6-dihydroprostacyclin produce only for a short time in ~~in~~ their aggregation inhibiting and blood pressure lowering activities. These compounds have therefore to

10 be administered in therapeutic use by continuous infusion. Apart from the spontaneous hydrolytic inactivation of natural prostacycline, the inactivation mechanisms which lead to the short active period of the chemically stable 5,6-dihydroprostacycline in vivo have only been explained in part at present.

Surprisingly the compounds of formula I produce considerably longer lasting effects than 5,6-dihydroprostacyclin, i.e. that they are suitable also for producing long lasting platelet aggregation inhibition and

15 blood pressure lowering on administration of single doses as may be seen from the following tables 2a and 2b:

Table 2a

Duration of the platelet aggregation inhibiting

20 effect in vivo (measured with the model of ADP induced fall in platelet count in narcotized rats on intravenous administration of the test compounds)

25	Test compound	Dose (mg/kg)	Maximum effect % Aggregation inhibition	effect in relation to maximum effect	
				10 min. after administration	30 min. after administration
30	5,6-Dihydroprostacyclin	0.1	62.4 = 100%	33.8%	0%
	Example 1e) 1)	1.0	72.7 = 100%	69.3%	41.3%
	Example 3b	0.1	72.5 = 100%	62.6%	66.3%
	Example 4b	1.0	66.8 = 100%	45.4%	24.5%

Table 2b

Blood pressure lowering effect
in conscious, spontaneous hypertensive rats

5	Test compound	Dose (mg/kg)	Maximum effect % Blood pressure lowering	effect in relation to maximum effect	
				10 min. after administration	30 min. after administration
10	5,6-Dihydroprostacyclin	0.0215	28 = 100%	7.1%	0 %
	Example 3b	0.1	23 = 100%	87.0%	39.1%
15	Example 4b	1.0	22 = 100%	90.9%	68.2%

Prostaglandins like PGE_2 or $\text{PGF}_{2\alpha}$ cause contraction of the smooth muscle of intestine and uterus and accordingly in-vivo may induce diarrhoea and abortion. Such effects are undesired side effects in compounds like analogs of prostacyclin to be used in platelet aggregation inhibition and in blood pressure lowering.

The new compounds of formula I in contrast to 5,6-dihydroprostacyclin have only very weak contraction inducing properties (as can be seen from the following tables 3a and 3b). Accordingly therapeutic use of doses sufficient to produce inhibition of platelet aggregation and lowering of the blood pressure causes no risk that such side effects may occur.

Table 3

Relative contraction-inducing activity in comparison with $\text{PGF}_{2\alpha}$ and 5,6-dihydroprostacyclin

a) tests on isolated rat uterus

Test compound	Relative contraction inducing activity
Prostaglandin $\text{F}_{2\alpha}$	100 % (EC_{50} 50.1 μM)
5,6-Dihydroprostacyclin	26.1 %
Product of Example 1e)i)	0.58 %

b) tests on isolated rat colon

Test compound	Relative contraction inducing activity
Prostaglandin $\text{F}_{2\alpha}$	100 % (EC_{50} 50.14 μM)
5,6-Dihydroprostacyclin	23.8 %
Product of Example 1e)i)	0.002%

Similar results were obtained also in testing other compounds of formula I.

As the compounds of formula I not only possess surprising valuable biological properties but also a good chemical stability they may be used for parenteral and also for oral application to humans and mammals to produce an inhibition of blood platelet aggregation in therapy and prophylaxis of diseases in which blood plate-

let aggregation and/or hyperaggregability are of patho-
genetic importance. Such diseases are for instance
arterial thromboses in vascular endothelial disorders,
atherosclerosis, hemostatic arterial and venous throm-
5 boses and myocardial infarction. Due to their influence
on the blood pressure the compounds of formula I are
suitable also for the treatment of pulmonary as well as
of systemic hypertension. The compounds according to
the invention are also useful for diminution of platelet
10 aggregability in extra-corporeal
circulation of blood (e.g. in dialysis,
cardiopulmonary bypass, etc.) wherein
the compounds are added in micromolar concentrations to
the patient's blood.

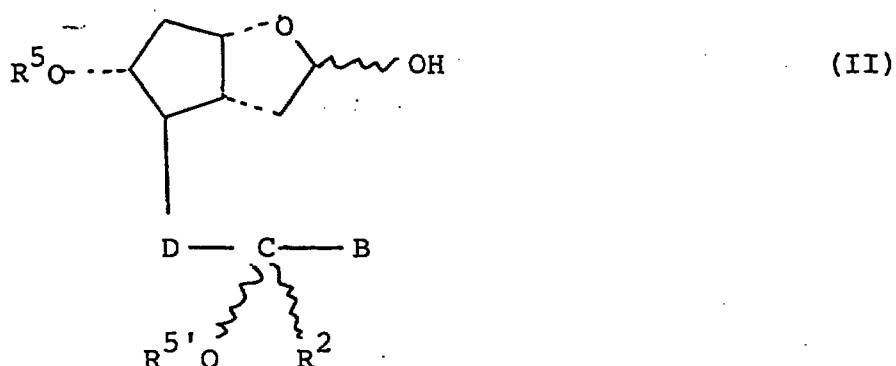
15 Another object of the invention accordingly
are medicaments (i.e. pharmaceutical compositions) con-
taining as active ingredient one or more of the hetero-
cyclic compounds of the invention. The active ingredient content of
the individual dose is 0.01 - 10 mg, whereby preferably
20 compositions for parenteral administration contain 0.01 -
1 mg and such for oral administration contain 0.1 - 10
mg. The medicaments to be used for parenteral adminis-
tration may be solutions or suspensions but also dry
formulations suitable for easy reconstitution as for
25 instance lyophilized sodium salts of compounds of formula
I in single dosage form.

Tablets, dragees or capsules can be used for oral
administration, and the active ingredients are optionally
mixed with conventional carriers, disintegrating agents,
binders, etc. and processed. Such forms of oral admini-
stration can also be produced in conventional manner such
that they have delayed release of the active ingredient
so as to ensure uniform supply of active ingredient to the
patient over a prolonged period. In this case, it is possible
to increase the above-mentioned dose, for example to 25 to
50 mg per individual form of the delay preparation, providing
that the rate of release is such that the level of active
ingredient in the blood is not higher than during oral
administration of a non-delayed form of preparation.

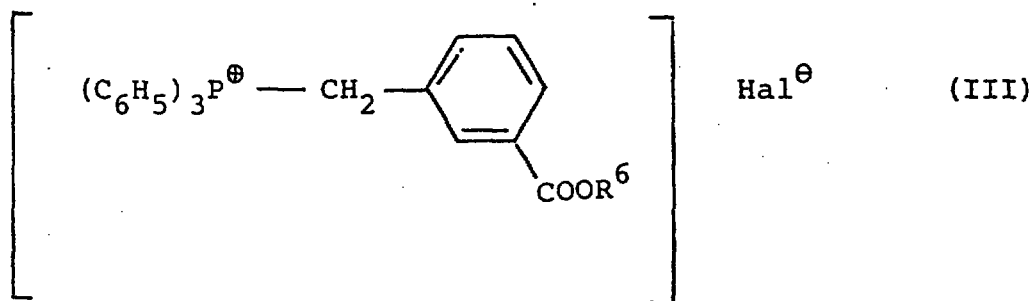
The pharmaceutical compositions are prepared
according to the invention

in a manner known per se. It should be mentioned that the compositions for parenteral use have to be in sterile and, if prepared in liquid form, isotonic condition.

- 5 A further object of the invention is the preparation of the compounds of formula I.
Firstly a lactol of the formula



- which may be in the 15S-form and wherein B and R² have
10 the same meaning as in formula I, D is a -CH₂-CH₂-,
(trans)-CH=CH- or -CH=CHal- group, in which Hal represents a chlorine, bromine or iodine atom, and wherein
R⁵ and R^{5'} have the same or a different meaning and
each represents hydrogen or a protecting group which
15 can be split off under mild conditions as for instance
a tetrahydropyranyl group (THP) or a trimethyl silyl
group (TMS) is reacted at about
10 to 30°C in presence of a solvent containing a strong
base and in absence of oxygen with a phosphonium salt
20 of the formula



wherein R^6 is hydrogen or a C_1 - C_6 alkyl radical, preferably methyl or ethyl, and wherein Hal represents a chlorine, bromine or iodine atom, preferably bromine,
 5 and - if R^6 is a hydrogen atom - the carboxyl group is converted into the methyl ester group by treatment with diazomethane in ether at about 0 to 30°C and finally if R^5 and $\text{R}^{5'}$ are protective groups they are split off under mild conditions. R^6 may be a straight-chained or branched alkyl radical, and is preferably methyl or ethyl.

10 Strong bases which may be added during the condensation reaction are especially butyl lithium, sodium hydride or potassium tert.- butylate which are used in presence of solvents such as, for example dimethylsulfoxide, ether, tetrahydrofuran and dimethylformamide.

15 The compound of formula III is used in an amount of 1 to 6 moles per mole of the compound of formula II, using 2 or more moles in the case when D represents the radical $-\text{CH}=\text{CHal}-$ because in this case under the conditions of the reaction this radical is
 20 transformed (with eliminating of the respective hydrogen halide) to the group $-\text{C}\equiv\text{C}-$.

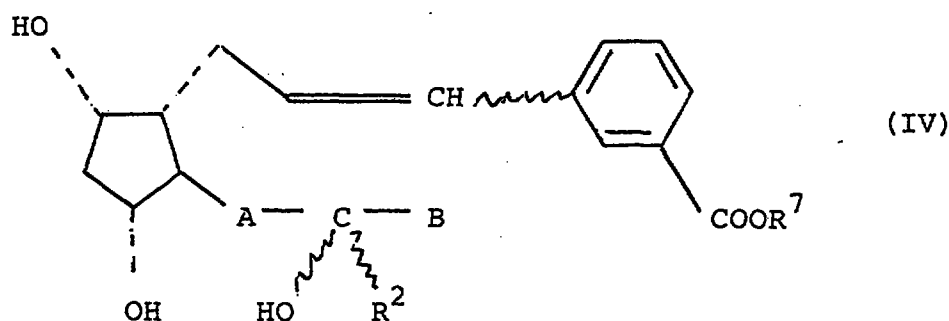
The presence of oxygen is especially prevented by working in an atmosphere of inert gases like argon or nitrogen.

25 The reaction is performed in about 1 to 12 hours and may be controlled as usual by chromatography.

To the reaction mixture preferably a small, catalytically effective amount of a lower aliphatic carboxylic acid is added such as formic acid, acetic acid, propionic acid, bromoacetic acid, trichloroacetic acid or tri-
 5 fluoroacetic acid or, for instance phenyl acetic acid, p-nitrobenzoic acid, p-chlorobenzoic acid or p-methoxybenzoic acid and especially the unsubstituted benzoic acid.

If R^5 or $R^{5'}$, respectively, represent protect-
 10 ing groups these may be split off by treating for 1 to 5 hours at 30 to 50°C with a mixture of tetrahydrofuran, glacial acetic acid and water in a ratio by volume of 1:3:1.

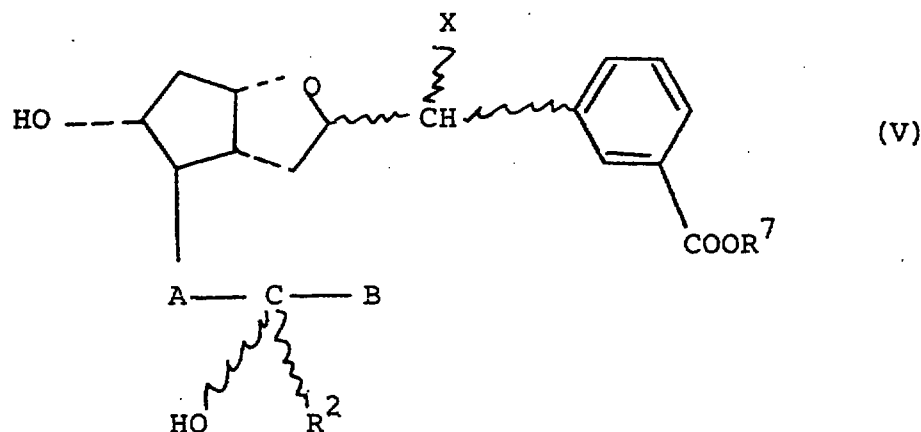
Thus a compound is obtained having the formula



15 wherein R^2 , A and B have the same meaning as in formula I and wherein R^7 is a C_1 - C_6 alkyl radical.

If desired this compound may be separated into the 15R- and 15S- forms by column chromatography with silica gel.

20 The obtained products of formula IV are then in a manner known per se halogenated and cyclized at a temperature of about 0 - 30°C with an electrophilic agent such as iodine, iodine-potassium iodide or N-bromosuccinimide in an inert solvent and optionally in the presence of water with addition of an acid-binding agent to give a compound of formula V:



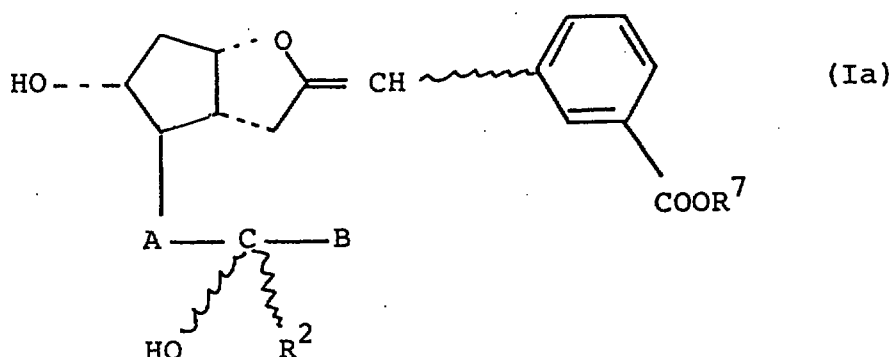
wherein R^2 , R^7 , A and B have the same meaning as above and wherein X represents a bromine or an iodine atom. Solvents which may be used in this reaction are for instance ethylether, tetrahydrofuran, dichloromethane, chloroform or mixtures of these solvents. The reaction is performed within about 30 minutes to 12 hours and its progress may be supervised as usual by

15 chromatography.

An acid-binding agent which may be used in this reaction is for instance sodium hydrogen carbonate, sodium carbonate, potassium carbonate, magnesium oxide or calcium carbonate.

5 Preferably X is an iodine atom and R^7 a methyl or an ethyl radical.

20 On treating the compound of formula V with 1 to 5 moles of a base at temperatures of 0 to 90°C for about 4 to 12 hours dehydrohalogenation occurs and a compound is formed having the formula:



wherein R², R⁷, A and B have the same meaning as above and the ester group COOR⁷ is optionally hydrolyzed to give a compound of formula I in which R¹ is hydrogen or a cation.

Preferably the reaction of the compound of formula V with the base occurs at 0 - 30°C. To induce the dehydrohalogenation the following bases are especially suitable: sodium hydroxide, potassium hydroxide, sodium methylate, sodium ethylate, potassium tert.-butylate as well as triethylamine, dicyclohexylamine, 1,5-diazabicyclo-(4.3.0)-non-5-ene (DBN) or 1,5-diazabicyclo-(5.4.0)-undec-5-ene (DBU). This reaction may be carried out in the absence or in the presence of a solvent such as toluene, methanol or ethanol.

The hydrolysis of the ester group COOR⁷ is preferably performed in aqueous-alcoholic solutions (like water-containing methanol or ethanol) at 10 to 50°C in presence of 1 to 5 moles of sodium- or potassium hydroxide, calculated on the amount of compound of formula Ia present in the reaction mixture. The reaction is completed in about 6 to 48 hours. It is also possible to perform the dehydrohalogenation and the hydrolysis of the ester group in the same reaction vessel without intermediate isolation of the compound of formula Ia.

The compounds of formula I in which R¹ is a cation obtained by hydrolysis of compounds of formula Ia may (if desired after separating the 5E- and 5Z-

isomers by means of high performance liquid chromatography (HPLC) using "reversed-phase"-conditions/ be transformed in a manner known per se into other salts for instance by ion exchange chromatography.

5 The starting materials of formulae II and III, respectively, are obtained as described in the literature or in an analogous manner as follows:

A) Phosphonium salts of formula III: Stoichiometric amounts of the respective aralkyl halogenides and of
10 triphenylphosphine are boiled in acetonitrile for 1½ hours with reflux. They are then concentrated in a rotary evaporator at 50 to 70°C in a vacuum and the solid residue is thoroughly washed with cold acetone and, if necessary, recrystallized from water. Thus e.g. the m-carboxyphenyl-
15 methyl triphenyl phosphoniumbromide melting at 256 - 258°C was obtained.

B) 3 α ,5 α -Dihydroxy-2 β [(3RS)-3-hydroxy-3-methyl-trans-1-octenyl]-cyclopentane-1 α -acetaldehyde γ -lactol 3-trimethylsilyl ether was obtained as described by
20 E.W. Yankee et al. in J.A.C.S. 96 5865 - 5876 (1974).

C) The preparation of the lactols required as starting materials of formula II is described in the following publications or may be made in an analogous manner,

25	15-Alkyl	E.W. Yankee <u>et al.</u> J.A.C.S. <u>96</u> 5865 (1974)
	15-H	E.J. Corey <u>et al.</u> J.A.C.S. <u>91</u> 5675 (1969)
	13,14-Dihydro	German Offenlegungsschrift No. 23 55 540
30	13,14-Dehydro	Belgian Patent No. 832 891
	16-Alkyl and	} German Offenlegungsschrift No. 22 17 044
	16,16-Dialkyl	
	15(4'-Alkylcyclohexyl)	Belgian Patent No. 782 822

The following examples serve further to illustrate the invention. All temperature references are uncorrected. The nuclear resonance spectra were measured (proton spectra at 60 MHz) with commercially available equipment. The R_f -values were determined by thin layer chromatography.

Example 1

- a) $\angle$ (5EZ, 13E, 9 α , 11 α , 15RS)-2,3,4-Trinor-1,5-inter-
m-phenylene-9,11,15-trihydroxy-15-methyl]-prosta-
5,13-dienoic acid.

1.8 ml of butyllithium (15% solution in hexane) are added dropwise with exclusion of humidity and under nitrogen at room temperature to 25 ml of dry dimethylsulfoxide and the mixture is stirred for 30 minutes. Thereafter, a solution of 670 mg of m-Carboxyphenylmethyl triphenyl phosphoniumbromide (general formula III: $R^6 = H$) and of 67 mg of benzoic acid in 10 ml of dry dimethyl sulphoxide is added dropwise.

15 minutes later a solution of 500 mg of 3 α ,5 α -dihydroxy-2 β - $\angle$ (3RS)-3-hydroxy-3-methyl-trans-1-oct-enyl]-cyclopentane-1 α -acetaldehyde γ -lactol-3-trimethylsilyl ether in 5 ml of dimethylsulfoxide is added dropwise. The reaction mixture is stirred at room temperature for 12 hours and then poured into a saturated solution of sodium chloride

The mixture is extracted three times with ethyl acetate, the organic phase being discarded. The aqueous solution is acidified to pH 4 by adding diluted hydrochloric acid and then extracted thoroughly several times with ethyl acetate. The thus obtained organic phases are washed with water, dried over magnesium sulfate and finally evaporated at 40°C in a vacuum, using a rotation evaporator.

The raw product (520 mg) is purified by column chromatography on silica gel using a mixture of ethyl acetate with glacial acetic acid in the proportion 99.5:0.5. Thus 300 mg of a slightly yellowish oil are obtained.

$R_f = 0.125$ (toluene - dioxane - glacial acetic acid 68 : 32 : 0.5)

Chemical shifts are given in ppm.

$^1\text{H-NMR}$ (CDCl_3): (0.87, t, 3H); (1.27, s, 3H); (3.63-4.36, m, 5H); (5.36-5.6, m, 2H); (5.6-6.5, m, 2H); (7.2-7.5, m, 2H); (7.5-8.03, m, 2H).

$^{13}\text{C-NMR}$ (methanol- d_4): 27.271 (15S-Me); 28.184 (15R-Me)

15 b) $\angle(5\text{EZ}, 13\text{E}, 9\alpha, 11\alpha, 15\text{RS})$ -2,3,4-Trinor-1,5-inter-m-phenylene-9,11,15-trihydroxy-15-methyl-7-prosta-5,13-dienoic acid methyl ester.

(General formula IV: $\text{R}^2 = \text{CH}_3$; $\text{R}^7 = \text{CH}_3$;

A = (trans)-CH=CH-; B = n- $\text{C}_{5}\text{H}_{11}$)

20 370 mg of the compound prepared according to example 1a are dissolved in 50 ml of diethylether. While stirring at room temperature this solution is treated with a solution of diazomethane in ether until the evolution of nitrogen ceases. Thereafter the yellow reaction mixture is treated with an aqueous solution of sodium hydrogen carbonate while stirring. The colourless ethereal extract is separated, dried over magnesium sulfate and evaporated under vacuum at 30°C in a rotary evaporator. The remaining slightly yellowish oil (350 mg) in thin layer chromatography gives two main spots having R_f 0.48 and 0.55, respectively, (di-

ethylether - acetonitril 3 : 2). By column chromatography of the crude product on silica gel with diethylether - acetonitrile 3 : 2 two isomeric compounds are obtained being the desired 15S-isomer and the 15R-isomer which becomes discarded.

The 15S-isomer is obtained in a yield of 130 mg. Its R_f -value is 0.48 (diethylether - acetonitrile 3 : 2).

$^1\text{H-NMR}$ (CDCl_3): (0.87, t, 3H); (1.27, s, 3H); (3.7-4.43, m, 3.9, s, 5H); (5.37-5.6, m, 2H); (5.6-6.73, m, 2H); (7.2-7.5, m, 2H); (7.67-8, m, 2H).

$^{13}\text{C-NMR}$ (methanol- d_4): 27.454

15 c) $[(13\text{E}, 5\text{RS}, 6\text{RS}, 9\alpha, 11\alpha, 15\text{S})-2,3,4\text{-Trinor-1,5-inter-m-phenylene-5-iodo-6,9-epoxy-11,15-dihydroxy-15-methyl}]/\text{-prost-13-enoic acid methyl ester.}$

(General formula V: $\text{R}^2 = \text{R}^7 = \text{CH}_3$; $\text{X} = \text{J}$; $\text{A} = (\text{trans})\text{-CH=CH-}$; $\text{B} = \text{n-C}_5\text{H}_{11}$)

20 To a solution of 720 mg of iodine in a mixture of 6 ml of diethyl ether and 2 ml of saturated sodium hydrogencarbonate solution is added rapidly at room temperature in the dark while stirring a solution of 170 mg of the product of example 1b in 2 ml of diethyl
25 ether. The reaction mixture is stirred in the dark at room temperature for 45 minutes and then treated with sodium thiosulfate solution until colourless. After pouring into an ice-cold aqueous saturated solution of sodium chloride the reaction mixture is three times
30 extracted with 20 ml of diethyl ether each time.

The ether phases are dried over magnesium sulphate

filtered, and finally evaporated in a rotation evaporator in a vacuum in the dark without heating. The crude product, obtained in form of 180 mg of a yellowish oil having $R_f = 0.58$ (ethyl acetate) is used in the next step without purification.

d) $\angle(5EZ, 13E, 9\alpha, 11\alpha, 15S)$ -2,3,4-Trinor-1,5-inter-m-phenylene-6,9-epoxy-11,15-dihydroxy-15-methyl/-prosta-5,13-dienoic acid methylester.

(General formula I: $R^1 = R^2 = CH_3$; A = (trans)-CH=CH-; B = $n-C_5H_{11}$).

180 mg of the compound obtained in example 1c are dissolved in 2 ml of toluene and, after addition of 100 μ l of DBN, stirred in the dark for 4 1/2 hours.

Thereafter the toluene is eliminated by a stream of nitrogen at room temperature. The residue by column chromatography on silica gel with ethyl acetate gives 90 mg of a slightly yellowish oil which consists of two components having R_f values of 0.55 and 0.6, respectively (ethyl acetate)

e) Sodium salt of $\angle(5EZ, 13E, 9\alpha, 11\alpha, 15S)$ -2,3,4-Trinor-1,5-inter-m-phenylene-6,9-epoxy-11,15-dihydroxy-15-methyl/-prosta-5,13-dienoic acid.

(General formula I: $R^1 = Na$; $R^2 = CH_3$; A = (trans)-CH=CH-; B = $n-C_5H_{11}$)

90 mg of the product obtained in example 1d are dissolved in 1 ml of methanol. After addition of 600 μ l of $1N$ -NaOH the mixture is stirred for 12 hours at 30 - 40°C.

R_f : 0.36 and 0.44 (silica gel RP-8, methanol - water 80 : 20). Silica gel RP-8 is a product of

the company Merck AG. Darmstadt, Germany. By high performance liquid chromatography using methanol - water 40 : 60 on silica gel RP-18 (a brand of Merck AG, Darmstadt, Germany) and lyophilization of the eluate there are obtained:

5

- i) Sodium salt of $\angle(5Z, 13E, 9\alpha, 11\alpha, 15S)$ -2,3,4-trinor-1,5-inter-m-phenylene-6,9-epoxy-11,15-dihydroxy-15-methyl]-prosta-5,13-dienoic acid

yield 35 mg

10

$R_f = 0.36$ (silica gel RP-8, methanol - water 80:20)

1H -NMR (methanol- d_4): (0.9,t,3H); (1.28,s,3H); (3.63-4.2,m,1H); (5.28,s,broadened, 1H); (5.5-5.73,m,2H); (7.06-7.48, m,1H); (7.53-7.8,m,2H); (7.96-8.1,m,1H).

15

- ii) Sodium salt of $\angle(5E, 13E, 9\alpha, 11\alpha, 15S)$ -2,3,4-trinor-1,5-inter-m-phenylene-6,9-epoxy-11,15-dihydroxy-15-methyl]-prosta-5,13-dienoic acid

Yield 18 mg

20

$R_f = 0.44$ (silica gel RP-8, methanol - water 80:20)

1H -NMR (methanol- d_4): (0.9,t,3H); (1.3,s,3H); (3.56-4.16,m,1H); (5.5-5.7,m,2H); (5.9,s, broadened, 1H); (7.13-7.48,m, 2H); (7.53-7.9,m,2H).

25

Example 2:

By using the procedure described in Example 1 and the appropriate starting materials there are obtained

30

- a) Sodium salt of $\angle(5E, 13E, 9\alpha, 11\alpha, 15S)$ -2,3,4-trinor-1,5-inter-m-phenylene-6,9-epoxy-11,15-

dihydroxy]-prosta-5,13-dienoic acid

(General formula I: $R^1 = \text{Na}$; $R^2 = \text{hydrogen}$; $A =$
(trans)-CH=CH-; $B = n\text{-C}_5\text{H}_{11}$)

5 $^1\text{H-NMR}$ (methanol- d_4): (0.9,t,3H); (1.3,s,3H); (3.6-
4.15,m,2H); (5.5-5.7,m,2H);
(5.85-6.05,s,broadened,1H);
(7.15-7.5,m,2H); (7.5-8,m,2H).

$R_f = 0.44$ (silica gel RP-8) methanol - water 80:20.

10 b) Sodium salt of $\angle(5Z, 13E, 9\alpha, 11\alpha, 15S)$ -2,3,4-trinor-
1,5-inter-m-phenylene-6,9-epoxy-11,15-dihydroxy]-
prosta-5,13-dienoic acid

(General formula I: $R^1 = \text{Na}$; $R^2 = \text{hydrogen}$; $A =$
(trans)-CH=CH-; $B = n\text{-C}_5\text{H}_{11}$)

15 $^1\text{H-NMR}$ (methanol- d_4): (0.9,t,3H); (3.5-4.1,m,3H);
(5.25,s,broadened, 1H); (5.45-
5.7,m,2H); (7-7.5,m,1H);
(7.5-7.85,m,2H); (8,s,broad-
ened, 1H).

$R_f = 0.34$ (silica gel RP-8) methanol - water 80:20

20 Example 3:

On following the procedure described in example 1
there are obtained from m-carboxyphenyl-methyl-tri-
phenyl-phosphonium bromide and the respective
compound of formula II:

25 a) Sodium salt of $\angle(5E, 13E, 9\alpha, 11\alpha, 15S)$ -2,3,4-tri-
nor-1,5-inter-m-phenylene-6,9-epoxy-11,15-di-
hydroxy-15-cyclohexyl-16,17,18,19,20-pentanor]-
prosta-5,13-dienoic acid.

(General formula I: $R^1 = \text{Na}$; $R^2 = \text{hydrogen}$; $A =$
(trans)-CH=CH-; $B = \text{cyclohexyl}$)

$^1\text{H-NMR}$ (methanol- d_4): (3.65-4.1, m, 3H); (5.5-5.7, m,
2H); (5.97, s, broadened, 1H);
5 (7.2-7.5, m, 2H); (7.5-8, m, 2H)

$R_f = 0.52$ (silica gel RP-8) methanol - water 80:20.

b) Sodium salt of [(5Z, 13E, 9 α , 11 α , 15S)-2,3,4-
trinor-1,5-inter-m-phenylene-6,9-epoxy-11,15-
dihydroxy-15-cyclohexyl-16,17,18,19,20-pentanor]-
10 prosta-5,13-dienoic acid.

(General formula I: $R^1 = \text{Na}$; $R^2 = \text{hydrogen}$; $A =$
(trans)-CH=CH-; $B = \text{cyclohexyl}$)

$^1\text{H-NMR}$ (methanol- d_4): (3.67-3.95, m, 2H); (4-4.2, m, 2H);
15 (5.37, s, broadened, 1H); (5.5-
5.7, m, 2H); (7.15-7.4, m, 1H);
(7.6-8.15, m, 3H).

$R_f = 0.38$ (silica gel RP-8) methanol - water 80:20.

Example 4:

20 By proceeding as described in the preceding examples
there are obtained:

a) Sodium salt of [(5E, 13E, 9 α , 11 α , 15S, 16RS)-2,3,4-
trinor-1,5-inter-m-phenylene-6,9-epoxy-11,15-
dihydroxy-16-ethyl]-prosta-5,13-dienoic acid.

25 (General formula I: $R^1 = \text{Na}$; $R^2 = \text{hydrogen}$;
 $A = (\text{trans})-\text{CH}=\text{CH}-$
 $B = -\text{C}(\text{R}^3, \text{R}^4)-(\text{CH}_2)_3-\text{CH}_3$,
wherein R^3 is C_2H_5 and R^4 is
hydrogen)

34

- 26 -

$^1\text{H-NMR}$ (methanol- d_4): (0.9, t, 6H); (3.6-4.2, m, 3H);
(5.5-5.7, m, 2H); (5.95, s,
broadened, 1H); (7.15-7.35,
m, 2H); (7.6-7.95, m, 2H).

5 $R_f = 0.68$ (silica gel RP-8) methanol - water 80:20.

b) Sodium salt of $\angle(5Z, 13E, 9\alpha, 11\alpha, 15S, 16RS)-2, 3, 4\text{-trinor-1, 5-inter-}m\text{-phenylene-6, 9-epoxy-11, 15-dihydroxy-16-ethyl-7-prosta-5, 13-dienoic acid}$

(General formula I: $R^1 = \text{Na}$; $R^2 = \text{hydrogen}$;

10

A = (trans)-CH=CH-;

B = -CH(C₂H₅)-(CH₂)₃-CH₃)

$^1\text{H-NMR}$ (methanol- d_4): (0.9, t, 6H); (3.75-4.55, m, 3H);
(5.35, s, broadened, 1H); (5.5-
5.7, m, 2H); (7.1-7.4, m, 1H);
15 (7.55-7.95, m, 1H); (8.05, m, 1H)

$R_f = 0.63$ (silica gel RP-8) methanol - water 80:20

Example 5:

The procedure is the same as described in example
1 whereby, however, m-carboxyphenylmethyl tri-
20 phenyl phosphoniumbromide and 3 α , 5 α -dihydroxy-2 β -
 $\angle(3RS)-3\text{-hydroxy-1-octyl-7-cyclopentane-1}\alpha\text{-ace-}$
talde γ -lactol bis-tetrahydropyranylether are used
as starting materials and there are obtained:

25 a) Sodium salt of $\angle(5E, 9\alpha, 11\alpha, 15RS)-2, 3, 4\text{-trinor-1, 5-inter-}m\text{-phenylene-6, 9-epoxy-11, 15-dihydroxy-7-prosta-5-enoic acid.}$

(General formula I: $R^1 = \text{Na}$; $R^2 = \text{hydrogen}$;

A = -CH₂-CH₂-; B = n-C₅H₁₁)

$^1\text{H-NMR}$ (methanol- d_4): (0.9,t,3H); (5.9,s,broadened, 1H); (7.18-8.15,m,4H);
No signal at 5.5-5.7.

$R_f = 0.48$ (silica gel RP-8) methanol - water 80:20.

- 5 b) Sodium salt of $\angle(5Z, 9\alpha, 11\alpha, 15RS)-2,3,4\text{-trino-}$
 $1,5\text{-inter-}\underline{m}\text{-phenylene-6,9-epoxy-11,15-dihydroxy-}$
 $\text{prosta-5-enoic acid.}$

(General formula I: $R^1 = \text{Na}$; $R^2 = \text{hydrogen}$

$A = -\text{CH}_2-\text{CH}_2-$; $B = n\text{-C}_5\text{H}_{11}$)

- 10 $^1\text{H-NMR}$ (methanol- d_4): (0.9,t,3H); (5.3,s,broadened, 1H); (7.1-8.05,m,4H);
No signal at 5.5-5.7.

$R_f = 0.41$ (silica gel RP-8) methanol - water 80:20.

- Following the procedures described above,
15 especially those explained in example I, the following
compounds of formula I are prepared:

Potassium salt of $\angle(5EZ, 13E, 9\alpha, 11\alpha, 15S)-2,3,4\text{-trino-}$
 $1,5\text{-inter-}\underline{m}\text{-phenylene-6,9-epoxy-11,15-dihydroxy-}$
 $\text{prosta-5,13-dienoic acid;}$

- 20 Sodium salt of $\angle(5EZ, 13E, 9\alpha, 11\alpha, 15S)-2,3,4\text{-trino-}$
 $1,5\text{-inter-}\underline{m}\text{-phenylene-6,9-epoxy-11,15-dihydroxy-16,16-}$
 dimethyl- $\text{prosta-5,13-dienoic acid;}$

- Potassium salt of $\angle(5EZ, 13E, 9\alpha, 11\alpha, 15S, 16RS)-2,3,4\text{-}$
 $\text{trino-1,5-inter-}\underline{m}\text{-phenylene-6,9-epoxy-11,15-dihydroxy-}$
25 16-ethyl- $\text{prosta-5,13-dienoic acid;}$

Potassium salt of $\angle(5EZ, 13E, 9\alpha, 11\alpha, 15S)-2,3,4\text{-trino-}$
 $1,5\text{-inter-}\underline{m}\text{-phenylene-6,9-epoxy-11,15-dihydroxy-15-}$
 $\text{cyclohexyl-16,17,18,19,20-pentanor-}$ $\text{prosta-5,13-dienoic}$

acid;

Sodium salt of $\angle(5EZ, 13E, 9\alpha, 11\alpha, 15S, 4'\text{-trans})\text{-}2,3,4\text{-}$
 $\text{trior-}1,5\text{-inter-}m\text{-phenylene-}6,9\text{-epoxy-}11,15\text{-dihydroxy-}$
 $15\text{-(}4'\text{-methyl-cyclohexyl)-}16,17,18,19,20\text{-pentanor}\text{-}$

5 prosta-5,13-dienoic acid;

Potassium salt of $\angle(5EZ, 13E, 9\alpha, 11\alpha, 15S, 4'\text{-trans})\text{-}2,3,$
 $4\text{-trior-}1,5\text{-inter-}m\text{-phenylene-}6,9\text{-epoxy-}11,15\text{-di-}$
 $\text{hydroxy-}15\text{-(}4'\text{-ethyl-cyclohexyl)-}16,17,18,19,20\text{-pentanor}\text{-}$
 prosta-5,13-dienoic acid;

10 Sodium salt of $\angle(5EZ, 9\alpha, 11\alpha, 15S)\text{-}2,3,4\text{-trior-}1,5\text{-}$
 $\text{inter-}m\text{-phenylene-}6,9\text{-epoxy-}11,15\text{-dihydroxy}\text{-prosta-}5\text{-}$
 $\text{en-}13\text{-ynoic acid};$

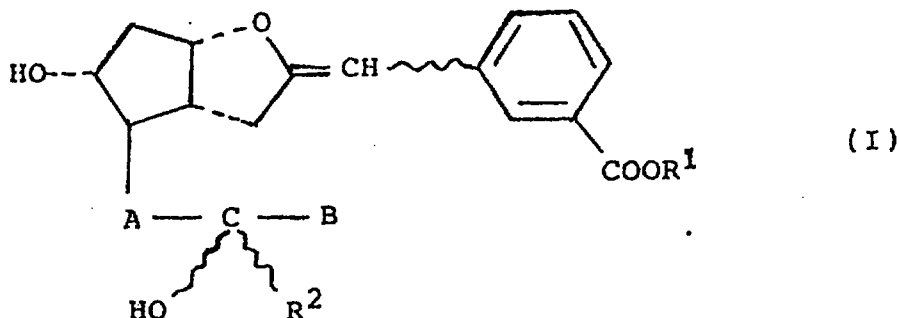
Sodium salt of $\angle(5EZ, 9\alpha, 11\alpha, 15S)\text{-}2,3,4\text{-trior-}1,5\text{-}$
 $\text{inter-}m\text{-phenylene-}6,9\text{-epoxy-}11,15\text{-dihydroxy-}15\text{-cyclo-}$
 15 hexyl-16,17,18,19,20-pentanor]-prosta-5-enoic acid;

Sodium salt of $\angle(5EZ, 9\alpha, 11\alpha, 15S)\text{-}2,3,4\text{-trior-}1,5\text{-}$
 $\text{inter-}m\text{-phenylene-}6,9\text{-epoxy-}11,15\text{-dihydroxy-}15\text{-cyclo-}$
 $\text{hexyl-}16,17,18,19,20\text{-pentanor}\text{-prosta-}5\text{-en-}13\text{-ynoic}$
 acid;

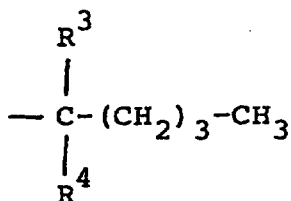
20 Sodium salt of $\angle(5EZ, 13E, 9\alpha, 11\alpha, 15S)\text{-}2,3,4\text{-trior-}$
 $1,5\text{-inter-}m\text{-phenylene-}6,9\text{-epoxy-}11,15\text{-dihydroxy-}15\text{-}$
 $\text{methyl-}15\text{-cyclohexyl-}16,17,18,19,20\text{-pentanor}\text{-prosta-}$
 $5,13\text{-dienoic acid.}$

CLAIMS (for Contracting States BE, CH, DE, FR, GB, IT, LI, LU, NL, SE)

1. Heterocyclic compounds corresponding to the following formula



in which the phenyl radical may have the E- and/or Z-configuration in regard to the double bond whilst the RS- or S-configuration may be present on the carbon atom 15 (carrying inter alia the radical R²) and in which R¹ represents a hydrogen atom, a pharmaceutically compatible cation or a linear or branched C₁-C₆ alkyl radical, R² represents hydrogen or methyl, A represents one of the groups -CH₂-CH₂-, (trans)-CH=CH- or -C=C- and B represents a C₅-C₉ alkyl radical having the following structure

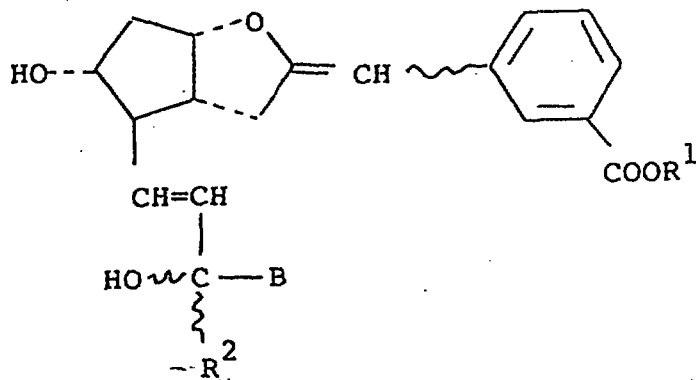


in which R³ and R⁴ may be the same or different and represent hydrogen, methyl or ethyl, or represents a cyclohexyl radical which may be substituted in the 4'-position by a methyl or ethyl radical.

2. Heterocyclic compounds as claimed in Claim 1

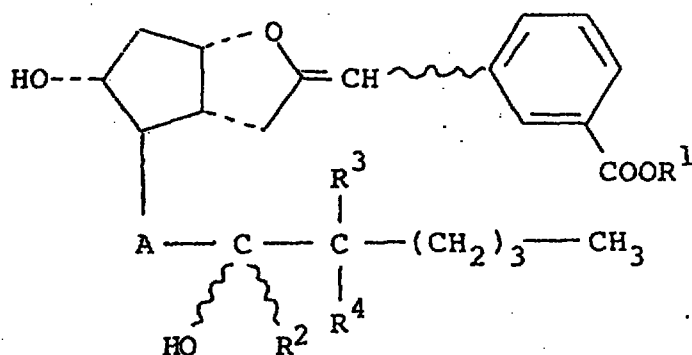


corresponding to the following formula



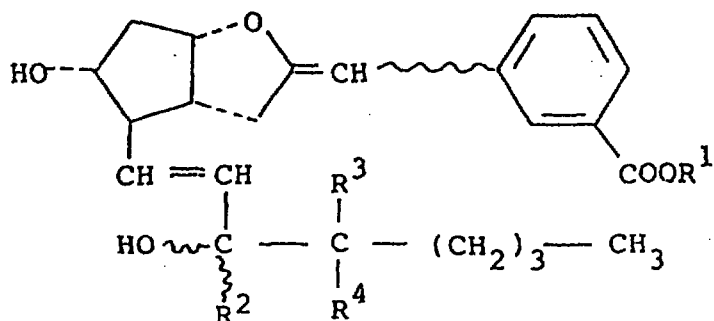
in which R^1 , R^2 and B have the same meaning as in formula I.

3. Heterocyclic compounds as claimed in Claim 1
5 corresponding to the following formula



in which R^1 to R^4 and A have the same meaning as in formula I.

4. Heterocyclic compounds as claimed in Claim 1
corresponding to the following formula

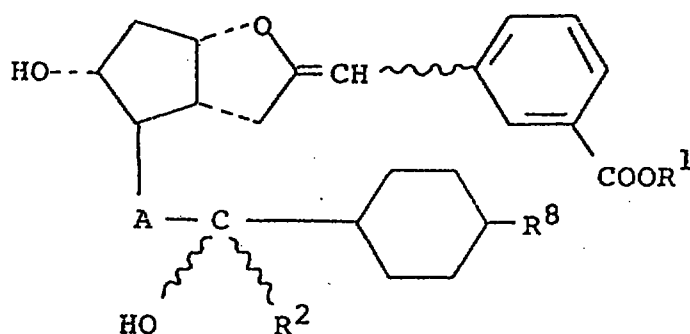


in which R^1 to R^4 have the same meaning as in formula I.

5. Heterocyclic compounds as claimed in Claim 1 to 4, in which R^3 and R^4 represent hydrogen.

5 6. Heterocyclic compounds as claimed in Claims 1 to 4, in which R^3 represents hydrogen and R^4 represents an ethyl radical.

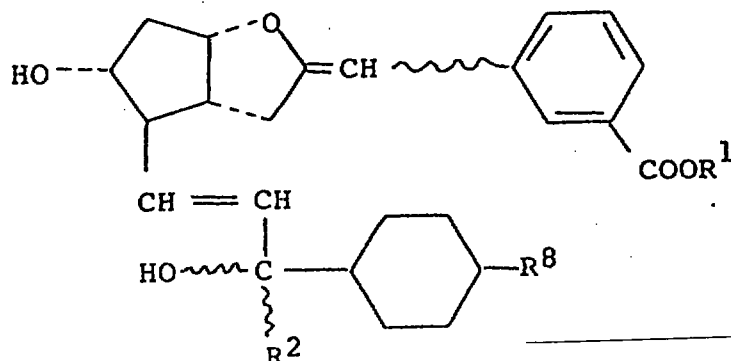
7. Heterocyclic compounds as claimed in Claim 1 corresponding to the following formula



10 in which R^1 , R^2 and A have the same meaning as in formula I and in which R^8 is hydrogen, methyl or ethyl.

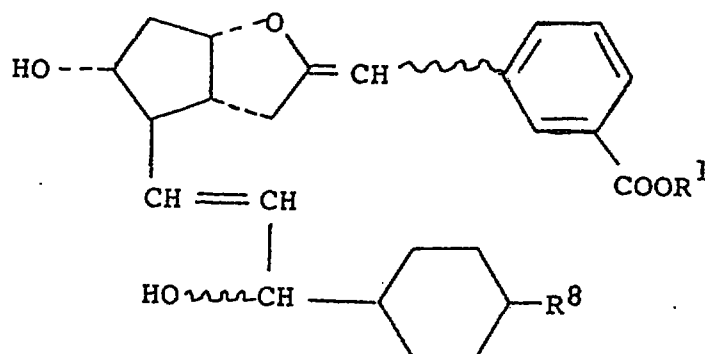
8. Heterocyclic compounds as claimed in Claim 1 to 7, in which R^2 represents hydrogen.

15 9. Heterocyclic compounds as claimed in Claim 1 corresponding to the following formula



in which R^1 and R^2 have the same meaning as in formula I and in which R^8 represents hydrogen, methyl or ethyl.

10. Heterocyclic compounds as claimed in Claim 1
5 corresponding to the following formula



in which R^1 has the same meaning as in formula I and in which R^8 represents hydrogen, methyl or ethyl.

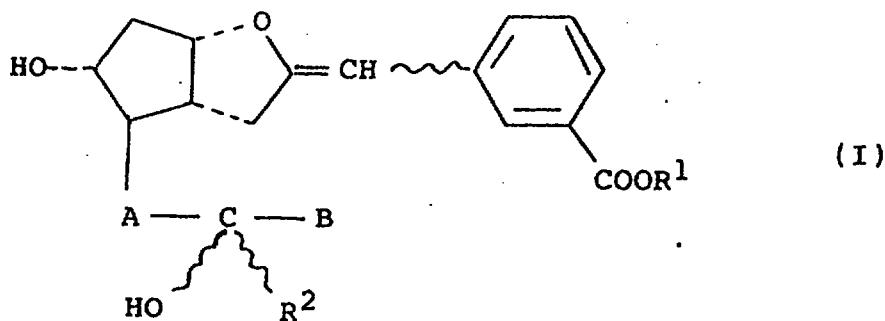
11. Heterocyclic compounds as claimed in Claims 1 to
10, in which R^1 represents a methyl or ethyl radical.
12. Heterocyclic compounds as claimed in claims 1 to 10, in which R^1 represents a sodium or potassium ion.
13. The 15 S-forms of the heterocyclic compounds
15 claimed in Claims 1 to 12.
14. The heterocyclic compound [(5EZ, 13E, 9 α , 11 α ,
20 15S)-2,3,4-trinor-1,5-inter-m-phenylene-6,9-epoxy-11,15-dihydroxy-15-methyl]-prosta-5,13-dienic acid claimed in Claim 1 and its pharmaceutically compatible salts, particularly its sodium salt, and its methyl ester.



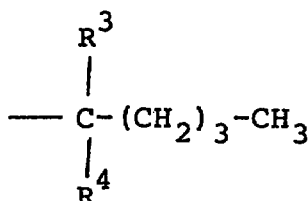
(41)

- 5 15. The heterocyclic compound [(5EZ, 13E, 9 α , 11 α , 15S)-2,3,4-trinor-1,5-inter-m-phenylene-6,9-epoxy-11,15-dihydroxy-15-cyclohexyl-16,17,18,19, 20-pentanor]-prosta-5,13-dienic acid claimed in Claim 1 and its pharmaceutically compatible salts, particularly its sodium salt, and its methyl ester.
- 10 16. A medicament, characterized in that it contains as active principle a heterocyclic compound of the type claimed in Claims 1 to 15.
17. A medicament as claimed in Claim 16, characterized in that it contains as active principle from 0.01 to 10 mg of a heterocyclic compound of the type claimed in Claims 1 to 15.
- 15 18. A medicament as claimed in Claims 16 and 17, characterized in that it is suitable for parenteral application and contains in a standard liquid sterile vehicle from 0.01 to 1 mg of a heterocyclic compound of the type claimed in Claims 1 to 15
- 20 in dissolved or suspended form.
19. A medicament as claimed in Claims 16 and 17, characterized in that it is in the form of tablets, dragees or capsules for oral application and contains from 0.1 to 10 mg of a heterocyclic compound of the type claimed in any of Claims 1
- 25 to 15 and standard excipients.
20. A process for producing heterocyclic compounds corresponding to the following formula





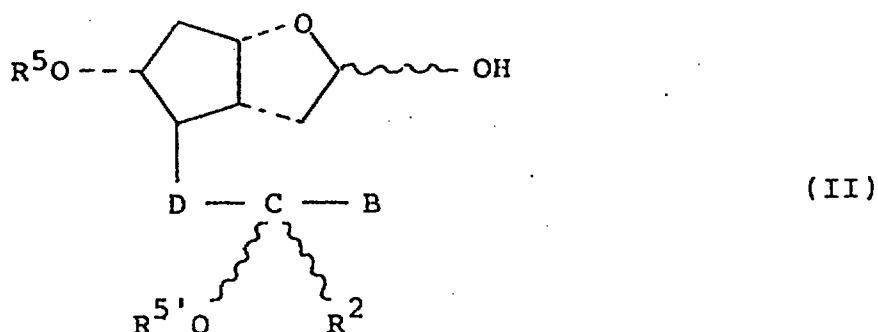
in which the phenyl radical may have the E- and/or Z-configuration in regard to the double bond whilst the RS- or S-configuration may be present on the carbon atom 15 (carrying inter alia the radical R^2) and in which R^1 represents a hydrogen atom, a pharmaceutically compatible cation or a straight-chain or branched C_1 - C_6 -alkyl radical, R^2 represents hydrogen or methyl, A represents one of the groups $-CH_2-CH_2-$, (trans)- $CH=CH-$ or $-C\equiv C-$ and B is a C_5 - C_9 -alkyl radical having the following structure



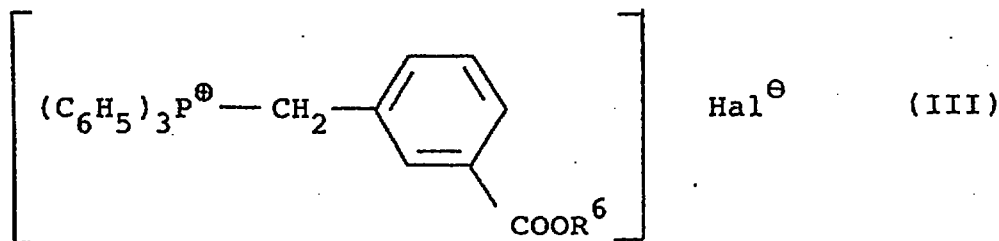
in which R^3 and R^4 may be the same or different and represent hydrogen, methyl or ethyl, or is a cyclohexyl radical which may be substituted in the 4'-position by a methyl or ethyl radical, characterized in that

a) a compound corresponding to the following formula





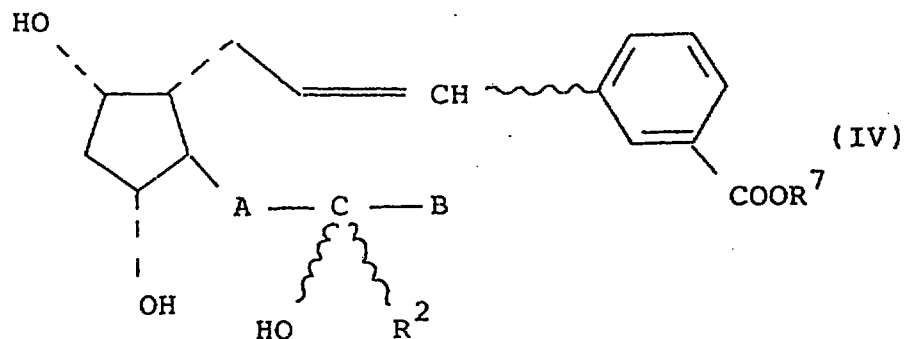
in which B and R² have the same meaning as in formula I, D is a -CH₂-CH₂-, trans-CH=CH- or -CH=CHal-group, where Hal is a chlorine, bromine or iodine atom, and in which R⁵ and R^{5'} may be the same or different and each represent a hydrogen atom or a protective group removable under mild conditions, more particularly a tetrahydropyranyl or trimethyl silyl group, is reacted with from 1 to 6 times the molar quantity of a compound corresponding to the following formula



in which R⁶ represents hydrogen or a C₁-C₆-alkyl radical, preferably a methyl or ethyl radical, and Hal is a chlorine, bromine or iodine atom, preferably a bromine atom, in the absence of oxygen at 10 to 30°C in the presence of a strong base and a solvent and, where R⁶ represents hydrogen, the carboxyl group COOR⁶ is then optionally esterified with diazomethane in ether at approximately 0 to 30°C and, where R⁵ and R^{5'} are protective groups, these protective groups are split off



under mild conditions, resulting in the formation of a compound corresponding to the following formula

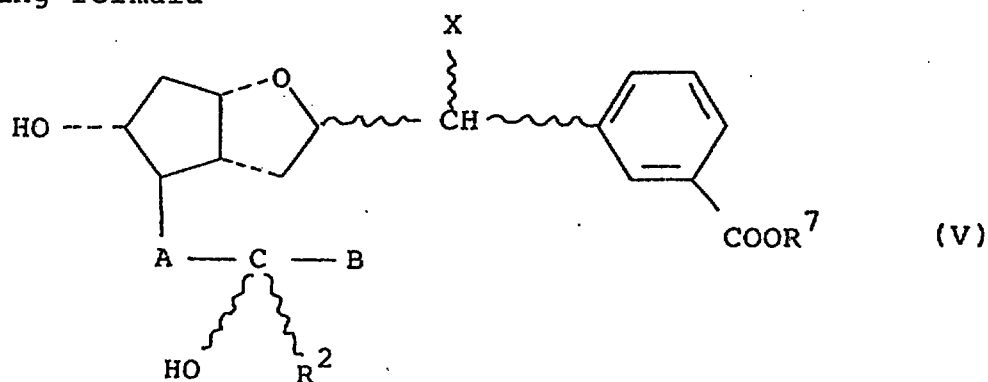


5

in which R^2 , A and B have the same meaning as in formula I and R^7 represents a C_1 - C_6 -alkyl radical, preferably a methyl or ethyl radical, the compound thus obtained

10

b) is halogenated at about 0 to 30°C in the presence of an inert solvent and optionally in the presence of an acid-binding agent and cyclized to form a compound corresponding to the following formula



15

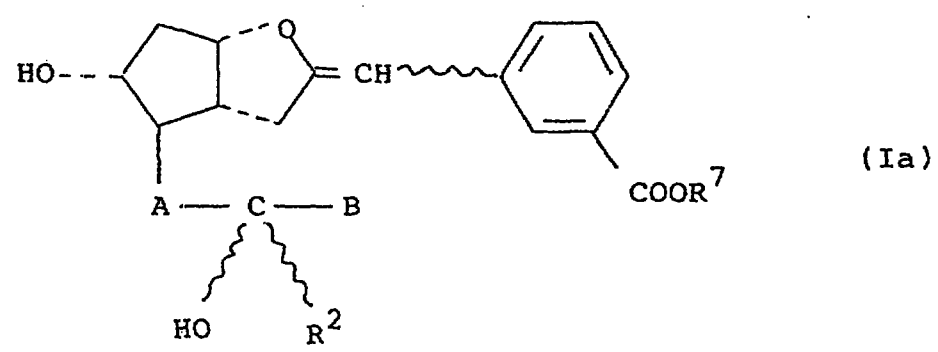
in which R^2 , R^7 , A and B have the same meaning as above and X represents bromine or iodine and

c) hydrogen halide HX is split off from the compound of formula V at temperatures of from



5

about 0 to 90°C with from 1 to 5 times the molar quantity of a base, optionally in the presence of a solvent, and the ester group COOR⁷ in the resulting compound which corresponds to the following formula



10

in which R², R⁷, A and B have the same meaning as above, is optionally hydrolyzed with an alkali hydroxide at around 10 to 50°C in aqueous-alcoholic solution and the resulting compounds of formula I are then preferably separated up into the 5E- and 5Z-isomers.

15

20

25

21. A process for the production of heterocyclic compounds as claimed in claim 20, characterized in that, in step a), the reaction of the compound corresponding to formula II with the compound corresponding to formula III is carried out in the presence of catalytic quantities of a carboxylic acid, preferably formic acid, acetic acid, propionic acid, bromoacetic acid, trichloroacetic acid, trifluoroacetic acid, phenyl acetic acid, p-nitrobenzoic acid, p-chlorobenzoic acid, p-methoxy benzoic acid and, more particularly, benzoic acid.
22. A process for the production of heterocyclic compounds as claimed in Claim 20, characterized in that, in step b), iodine, iodine-potassium



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- 10 -

5 iodide or bromosuccinimide, optionally in the presence of water and sodium hydrogen carbonate, sodium carbonate, magnesium oxide or calcium carbonate, is used for halogenating and cyclizing the compound corresponding to formula IV.

10 23. A process for the production of heterocyclic compounds as claimed in Claim 20, characterized in that, in step c) the hydrogen halide HX is split off by means of sodium hydroxide, potassium hydroxide, sodium methylate, sodium ethylate, potassium-tert.-butylate, triethylamine, dicyclohexylamine, 1,5-diazabicyclo-(4.3.0)-non-5-ene or 1,5-diazabicyclo-(5.4.0)-undec-5-ene.

15 24. A process for the production of heterocyclic compounds as claimed in Claims 20 and 23, characterized in that, in step c), the hydrogen halide HX is split off and the ester group COOR⁷ hydrolyzed without intermediate isolation of the compound corresponding to formula Ia.

20 25. A process for the production of heterocyclic compounds corresponding to general formula I in the form of the 15S-isomers as claimed in Claim 20, characterized in that the RS-forms of the compound of formula II, IV, V or Ia or I are
25 separated up in known manner, more particularly by column chromatography.

30 26. A process as claimed in Claims 20 and 25, characterized in that the compound of formula IV obtained in step a) is separated up into the 15S- and the 15R-forms by column chromatography, preferably using silica gel, and thereafter only the 15S-form of the compound of formula IV is used in step b).



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27. A process for the production of heterocyclic compounds as claimed in Claim 20, characterized in that in the compounds of formula I, in which R¹ represents a cation, this cation is replaced by another pharmaceutically compatible cation by ion exchange chromatography.
- 5

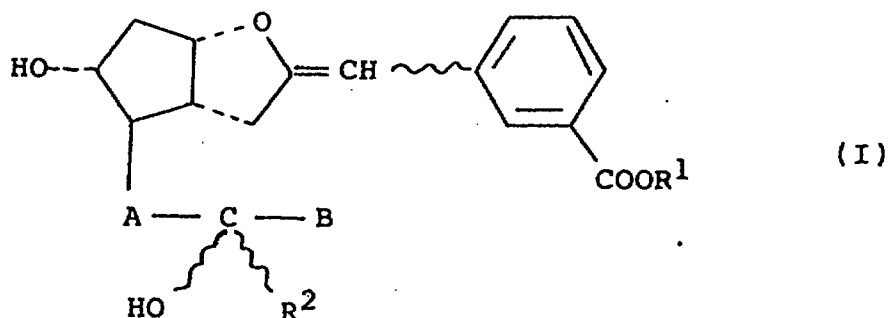


* C L M S *

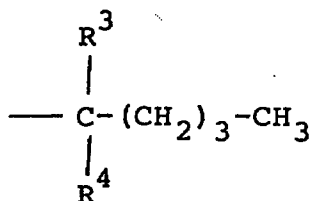
CLAIMS (for Contracting State AT)

FB

1. A process for the production of heterocyclic compounds corresponding to the formula



in which the phenyl radical may have the E- and/or Z-configuration in regard to the double bond whilst the RS- or S-configuration may be present on the carbon atom 15 (carrying inter alia the radical R^2) and in which R^1 represents a hydrogen atom, a pharmaceutically compatible cation or a straight-chain or branched C_1 - C_6 -alkyl radical, R^2 represents hydrogen or methyl, A represents one of the groups $-CH_2-CH_2-$, (trans)- $CH=CH-$ or $-C\equiv C-$ and B is a C_5 - C_9 -alkyl radical having the following structure

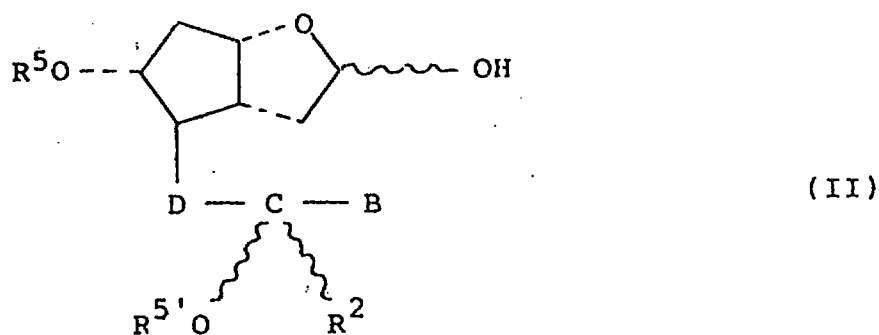


in which R^3 and R^4 may be the same or different and represent hydrogen, methyl or ethyl, or is a cyclohexyl radical which may be substituted in the 4'-position by a methyl or ethyl radical, characterized in that

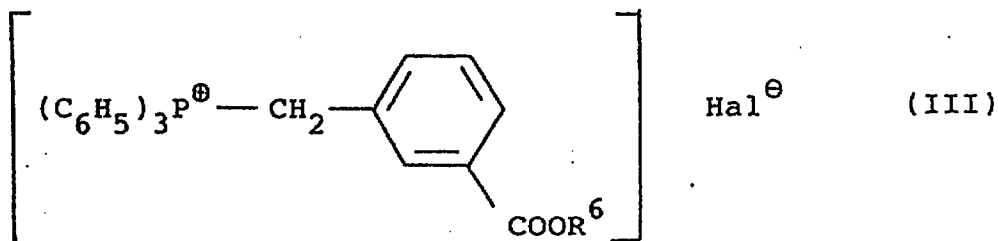
- a) a compound corresponding to the following formula



(49)



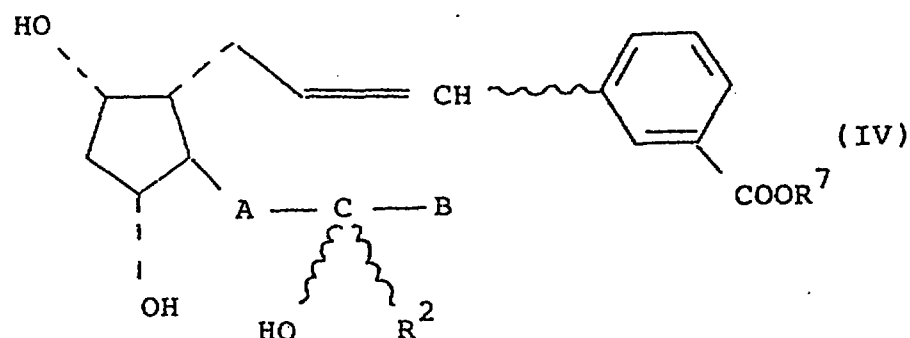
in which B and R² have the same meaning as in formula I, D is a -CH₂-CH₂-, trans-CH=CH- or -CH=CHal-group, where Hal is a chlorine, bromine or iodine atom, and in which R⁵ and R^{5'} may be the same or different and each represent a hydrogen atom or a protective group removable under mild conditions, more particularly a tetrahydropyranyl or trimethyl silyl group, is reacted with from 1 to 6 times the molar quantity of a compound corresponding to the following formula



in which R⁶ represents hydrogen or a C₁-C₆-alkyl radical, preferably a methyl or ethyl radical, and Hal is a chlorine, bromine or iodine atom, preferably a bromine atom, in the absence of oxygen at 10 to 30°C in the presence of a strong base and a solvent and, where R⁶ represents hydrogen, the carboxyl group COOR⁶ is then optionally esterified with diazomethane in ether at approximately 0 to 30°C and, where R⁵ and R^{5'} are protective groups, these protective groups are split off

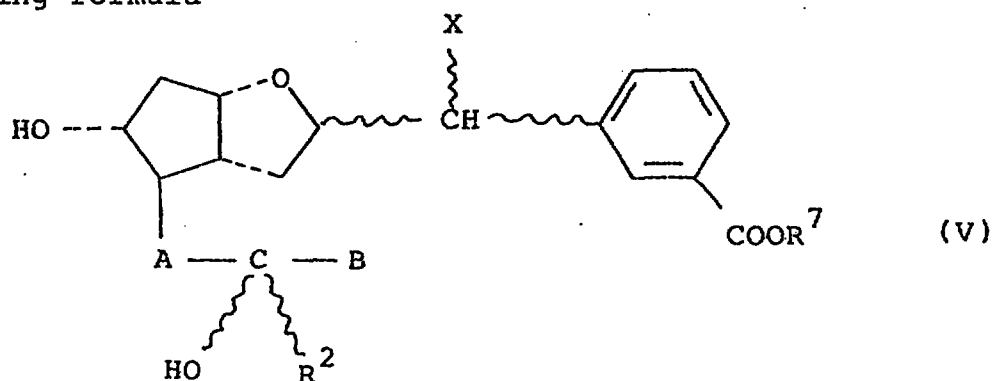


under mild conditions, resulting in the formation of a compound corresponding to the following formula



in which R^2 , A and B have the same meaning as in formula I and R^7 represents a C_1 - C_6 -alkyl radical, preferably a methyl or ethyl radical, the compound thus obtained

b) is brominated or iodinated at about 0 to 30°C in the presence of an inert solvent and optionally in the presence of an acid-binding agent and cyclized to form a compound corresponding to the following formula

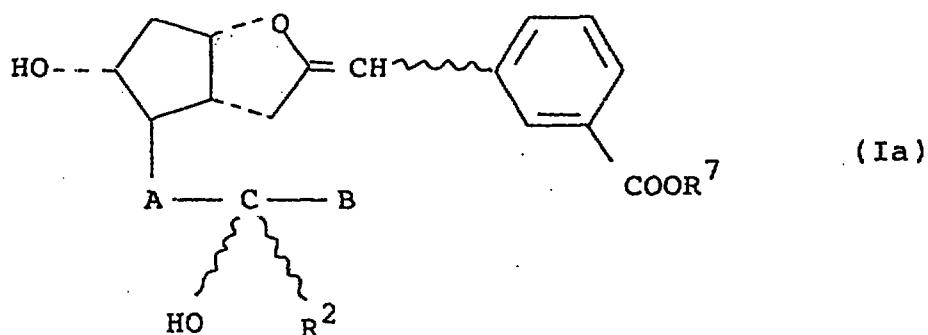


in which R^2 , R^7 , A and B have the same meaning as above and X represents bromine or iodine and

c) hydrogen halide HX is split off from the compound of formula V at temperatures of from



about 0 to 90°C with from 1 to 5 times the molar quantity of a base, optionally in the presence of a solvent, and the ester group COOR⁷ in the resulting compound which corresponds to the following formula



in which R², R⁷, A and B have the same meaning as above, is optionally hydrolyzed with an alkali hydroxide at around 10 to 50°C in aqueous-alcoholic solution and the resulting compounds of formula I are then preferably separated up into the 5E- and 5Z-isomers.

2 . A process for the production of heterocyclic compounds as claimed in claim 1, characterized in that, in step a), the reaction of the compound corresponding to formula II with the compound corresponding to formula III is carried out in the presence of catalytic quantities of a carboxylic acid, preferably formic acid, acetic acid, propionic acid, bromoacetic acid, trichloroacetic acid, trifluoroacetic acid, phenyl acetic acid, p-nitrobenzoic acid, p-chlorobenzoic acid, p-methoxy benzoic acid and, more particularly, benzoic acid.

3. A process for the production of heterocyclic compounds as claimed in Claim 1, characterized in that, in step b), iodine, iodine-potassium



5 iodide or bromosuccinimide, optionally in the presence of water and sodium hydrogen carbonate, sodium carbonate, magnesium oxide or calcium carbonate, is used for halogenating and cyclizing the compound corresponding to formula IV.

10 4. A process for the production of heterocyclic compounds as claimed in Claim 1, characterized in that, in step c) the hydrogen halide HX is split off by means of sodium hydroxide, potassium hydroxide, sodium methylate, sodium ethylate, potassium-tert.-butylate, triethylamine, dicyclohexylamine, 1,5-diazabicyclo-(4.3.0)-non-5-ene or 1,5-diazabicyclo-(5.4.0)-undec-5-ene.

15 5. A process for the production of heterocyclic compounds as claimed in Claims 1 and 4, characterized in that, in step c), the hydrogen halide HX is split off and the ester group COOR⁷ hydrolyzed without intermediate isolation of the compound corresponding to formula Ia.

20 6. A process for the production of heterocyclic compounds corresponding to general formula I in the form of the 15S-isomers as claimed in Claim 1, characterized in that the RS-forms of the compound of formula II, IV, V or Ia or I are
25 separated up in known manner, more particularly by column chromatography.

30 7. A process as claimed in Claim 1 and 6, characterized in that the compound of formula IV obtained in step a) is separated up into the 15S- and the 15R-forms by column chromatography, preferably using silica gel, and thereafter only the 15S-form of the compound of formula IV is used in step b).



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5 8. A process for the production of heterocyclic compounds as claimed in Claim 1, characterized in that in the compounds of formula I, in which R¹ represents a cation, this cation is replaced by another pharmaceutically compatible cation by ion exchange chromatography.

