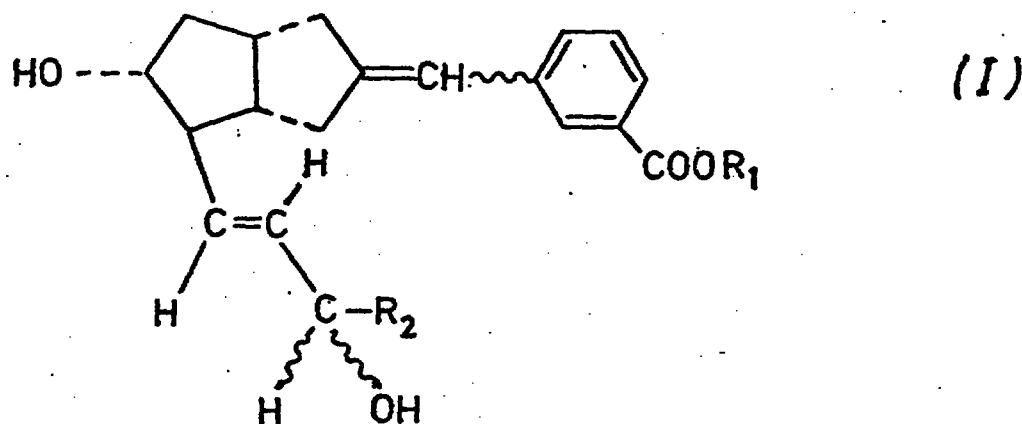


CIS-BICYCLO [3.3.0] OCTANE DERIVATIVES, MEDICINES CONTAINING THEM AND PROCESS FOR THE PREPARATION OF THESE COMPOUNDS AND THESE MEDICINES

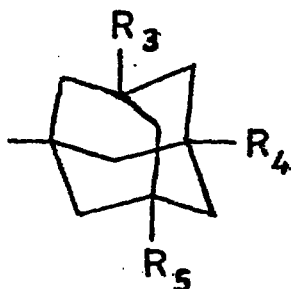
The present invention relates to new cis-bicyclo[3.3.0] octane derivatives of the formula I



in which the phenyl radical may have the EZ- or E-configuration with respect to the double bond and at the carbon atom which carries the group R_2 (and others) the molecule has the RS- or S-configuration.

In formula I, R_1 represents a hydrogen atom, a straight or branched alkyl group containing 1 to 4 carbon atoms or a pharmaceutically acceptable cation, and R_2 represents a cyclohexyl or 4-methylcyclohexyl radical or a 1-adamantyl radical of the

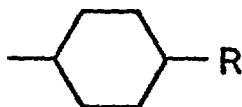
structure



wherein R_3 , R_4 and R_5 are the same or different and represent hydrogen or methyl.

Preferably R_1 represents hydrogen, a methyl or an ethyl radical or a sodium or a potassium ion. Other suitable cations are known especially from their use in the chemistry of prostaglandins or prostacyclin, respectively.

Preferably R_2 represents the group



wherein R is hydrogen or methyl and especially preferred for R_2 is the unsubstituted cyclohexyl group.

The compounds of formula I have valuable pharmacological properties. Thus they especially have blood platelet aggregation inhibiting effects and also blood pressure lowering activity, i.e. they have prostacyclin-like properties. They differ, however, from prostacyclin, for instance, in that they are far more stable than prostacyclin.

There are known already analogues of prostacyclin, which are chemically relatively stable, like carbacyclin (which like the compounds of formula I contains the cis-bicyclo[3.3.0]octane moiety) but these are nevertheless only short acting agents like prostacyclin when used in-vivo [c.f. Whittle et al., Prostaglandins 19 (1980), 605 - 627, especially page 623].

When compared with these known substances the compounds of formula I surprisingly not only show considerably prolonged action in-vivo but they also produce blood pressure lowering effects only after administering far higher dosages than those necessary to produce platelet aggregation inhibition. Accordingly the compounds of formula I can be used not only in diseases in which an inhibition of platelet aggregation is desired without 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, i.e. a blood pressure lowering effect, is desired (as for instance ischaemic peripheral vascular disease). These valuable properties may be demonstrated for instance by the experimentally-obtained values given hereinafter.

In Belgian Patent Specification No. 887721 (Example 13) there are described the E- and the Z-forms of 1,5-inter-m-phenylene-2,3,4-trinorcarbacyclin, i.e. of 3-(m-carboxybenzylidene)-6 β -(3'S-hydroxy-1E-octenyl)-7 α -hydroxy-cis-bicyclo[3.3.0]octane. The EZ-form of this compound (hereinafter referred to as "compound A") in some of the tests to be described hereinafter was used as an additional reference compound whereby surprisingly the compounds of formula I, especially those in which R₂ is cyclohexyl, showed also superior effects in comparison to those produced by compound A.

The enzyme adenylate cyclase catalyzes the formation of adenosine 3',5'-cyclic monophosphate (c-AMP) from adenosine triphosphate (ATP). If the adenylate cyclase in thrombocytes is stimulated by substances like prostacyclin, the c-AMP content of the thrombocytes is considerably increased whereby an aggregation of the thrombocytes is prevented. The following table 1 shows the degrees of stimulation of adenylate cyclase in horse thrombocytes induced by some of the compounds of formula I in comparison to the effects caused by 5,6-dihydroprostacyclin or by compound A, respectively:

Table 1

Test compound	EC* _{200%} $\mu\text{Mol/l}$	relative activity
5,6-Dihydroprostacyclin	15.0	1.0
Compound A	0.40	37.5
Example 1e	0.15	100.0
Example 2	0.13	115.4
Example 3e	0.18	83.3

*Dose causing a threefold stimulation of the c-AMP formation from ATP.

The aggregation of human thrombocytes induced by arachidonic acid in vitro may be inhibited e.g. by prostacyclin.

Table 2 shows the values of the IC_{50} (i.e. the concentration causing under the experimental conditions in 50% of the cases inhibition of the platelet aggregation) and also the relative activity in comparison to prostacyclin for some known compounds and for the products of Examples 1e and 2:

Table 2

Test compound	IC ₅₀ μ Mol/l	relative activity
Prostacyclin	0.0078	1.0
5,6-Dihydroprosta- cyclin	0.18	0.043
Compound A	0.12	0.065
Example 1e	0.08	0.098
Example 2	0.07	0.11

In addition reference is made to the findings of Whittle et al. (loc.cit., page 611) that as an inhibitor of the platelet aggregation induced by arachidonic acid in vitro carbacylin is only 0.02 times as active as prostacyclin.

Table 3 shows the activity of some compounds on the ADP induced fall in platelet count in vivo in narcotized rats (urethane narcosis) on intravenous administration of the test compounds.

Table 3

Test compound	relative activity
5,6-Dihydroprosta-	
cyclin	1.0
Compound A	0.1
Example 1e	1.0
Example 2	1.0

Tables 1 to 3 demonstrate the good blood platelet aggregation inhibiting effect of the compounds of formula I. As already mentioned these compounds 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 4a and 4b (the ED₂₀ is the dose causing a drop of the diastolic blood pressure by 20 mm Hg):

Table 4a

Blood pressure lowering activity in conscious, spontaneous hypertensive rats (measurement via in-dwelling catheter, intravenous administration of the test compounds):

Test compound	ED ₂₀ mg/kg	relative activity
5,6-Dihydroprosta- cyclin	0.005	1.0
Compound A	1.9	0.003
Example 1e	0.073	0.068
Example 2	0.094	0.053
Example 3e	> 1.0	< 0.005

Table 4b

Blood pressure lowering activity in narcotized rats (pentobarbital narcosis; intravenous administration of the test compounds):

Test compound	ED ₂₀ mg/kg	relative activity
Prostacyclin	0.16	1.0
Example 2	5.39	0.03

Both prostacyclin and carbacyclin are rapidly metabolized in vivo to inactive compounds and accordingly produce only for a short time their aggregation inhibiting and blood pressure lowering activities. In comparison thereto the compounds of formula I produce considerably longer lasting effects as may

be seen from the following Tables:

Table 5

On intravenous administration of a supra-maximal hypotensive dose (1mg/kg) of the test compounds in narcotized rats (pento-barbital narcosis) the following persistence characteristics of the blood pressure lowering activity ("b.p.l.a.") were observed:

Test compound	rate of decay of the b.p.l.a. in % per min.	half time of b.p.l.a. (min.)
Prostacyclin	11.0	5.89
Example 2	2.6	25.96

As can be seen therefrom the product of Example 2 acts about 5 times longer than prostacyclin. Also with respect to the thrombocyte aggregation inhibiting activity the considerably extended duration of the effect of the product of Example 2 could be demonstrated. In this experiment the substance was administered orally in a dose of 4.64 mg/kg to narcotized rats (urethane narcosis). The time dependent course of the thrombocyte aggregation inhibiting activity was determined (ADP aggregation in vivo; parameter for the determination: ADP induced fall in thrombocyte count, determined by a "Technicon Autocounter"). The following table shows the aggregation inhibition in percent at the respective times of determination:

	Time after administration (min)		
	30	60	150
% inhibition of aggregation	38	26	22

Oral administration of the product of Example 2 therefore causes a strong thrombocyte aggregation inhibition for at least 2.5 hours, whereas prostacyclin, for instance, is known to be ineffective on oral administration.

Since the compounds of formula I not only possess surprising and valuable biological properties but also a good chemical stability, they may be used for parenteral and also for oral application to humans to produce an inhibition of blood platelet aggregation in therapy and prophylaxis of diseases in which blood platelet aggregation and/or a hyper-aggregability are of pathogenetic importance. Such diseases are, for instance, arterial thromboses in vascular endothelial disorders, atherosclerosis, hemostatic arterial and venous thromboses 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 useful also for diminution of platelet aggregability in extra-corporeal circulations (e.g., in dialysis, cardio-pulmonary bypass etc.) wherein the compounds are added in micromolar concentrations to the patient's blood.

Furthermore the compounds of formula I cause a diminution of the secretion of gastric acid. Accordingly they may be used also in therapy and prophylaxis of diseases in which the se-

cretion of gastric acid is increased (e.g. gastric and duodenal ulcers as well as in the therapy of ulcers of other genesis (e.g. ulcers caused by the administration of antiphlogistics)).

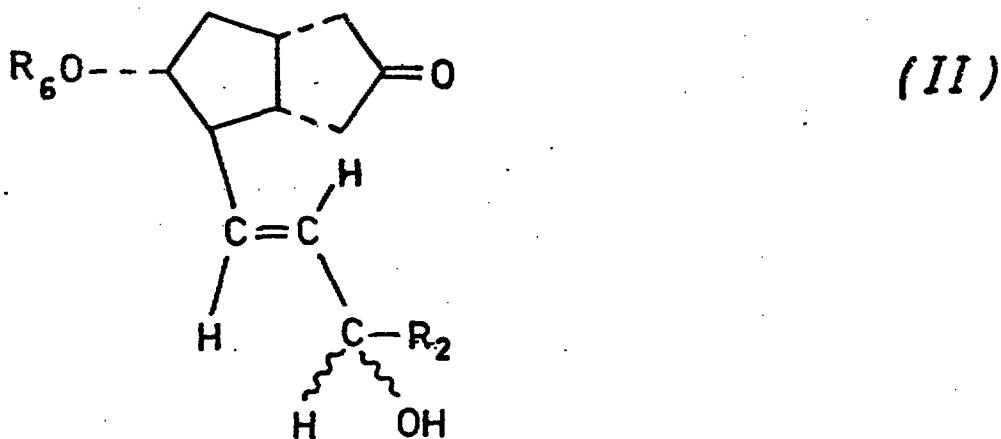
The invention accordingly also relates to medicaments (i.e. pharmaceutical compositions) containing as active ingredients one or more of the compounds of the invention. The amount of active ingredient per unit dose is between 0.01 and 50 mg, and compositions for parenteral administration contain 0.01 - 10 mg and compositions for oral administration contain 0.1 to 50 mg. The medicaments for parenteral administration may be solutions or suspensions but may also be spray formulations e.g. for intranasal application or may be dry formulations suitable for easy reconstitution, as for instance, lyophilized sodium salts of compounds of formula I in unit dosage form.

For oral administration, tablets, dragees or capsules are used, whereby the active ingredients optionally are mixed or worked up with the usual carrier materials, tablet disintegrating agents, binders etc. Such oral administration forms can also be prepared in customary manner so that release of the active ingredient is delayed, thereby ensuring uniform treatment of the patient with the active ingredient over a long period. In this case it is possible to increase the amount mentioned above of the active compound contained in the unit dose for example to 100 or 250 mg for the unit dosage form, provided, that the rate of release of the active ingredient is such that the resulting blood level of the active ingredient is not higher than that obtained on oral administration of a dosage form without delayed release.

These pharmaceutical compositions are prepared according to the invention in a manner known per se, whereby care is taken to ensure that the compositions for parenteral use are sterile,

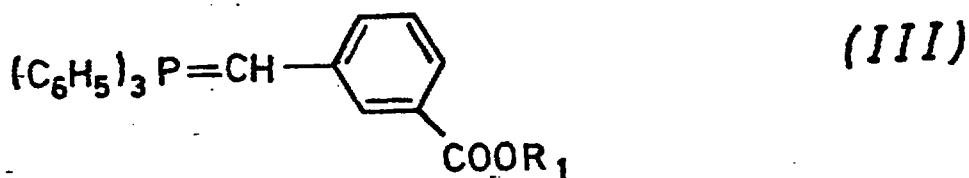
and isotonic when in liquid form.

A further aspect of the invention is the preparation of the compounds of formula I which comprises reacting a compound of the general formula II



wherein R_2 has the same meaning as above and R_6 is a hydrogen atom or a protecting group which can be split off under mild conditions,

with a compound of formula III



wherein R_1 has the same meaning as above and subsequently, optionally splitting off the group R_6 , if different from hydrogen. Preferred protecting groups represented by R_6 in the compound of formula II are a tetrahydropyranyl group or a trialkylsilyl group containing in the alkyl radicals a total of 3 - 6 carbon atoms, but benzoyl- or p-phenylbenzoyl radicals and other protecting groups commonly used in prostaglandin chemistry may also be used as protecting groups.

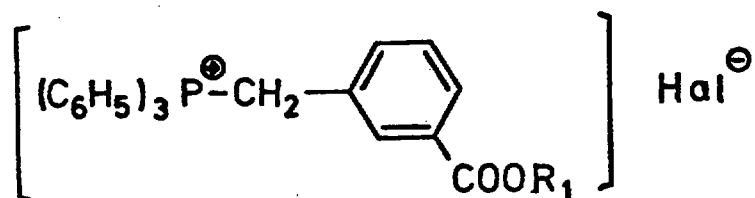
The compound of the general formula II is reacted with the compound of formula III, while carefully excluding humidity and in an atmosphere of inert gases such as argon or nitrogen which are particularly suitable, in the presence of an inert aprotic solvent such as benzene, toluene, dimethylsulfoxide or dimethylformamide. The reaction is carried out at a temperature between about 0°C and 100°C, preferably in benzene at a temperature between 20°C and 60°C. It is appropriate to add a small amount of a weakly acidic compound such as thiophenol, p-chloro-thiophenol, thiocresol or similar compounds.

Thus compounds of formula I in the form of the EZ isomeric mixture are obtained. If R_1 is an alkyl radical it is possible (optionally after separation of the isomers) to saponify the group COOR_1 to the carboxy group ($R_1 = \text{H}$) and, if desired, to convert the compound obtained into a pharmaceutically acceptable salt. However, saponification or salt formation can also be carried out at first, followed by separation of the isomers. If, however, R_1 is hydrogen and there are desired compounds of formula I in which R_1 is one of the alkyl radicals defined above it is possible to esterify the compound first obtained in a manner known per se, optionally after previous separation of the isomers.

The separation of the E- and Z-isomers is effected by high performance liquid chromatography (HPLC) in a manner known per se

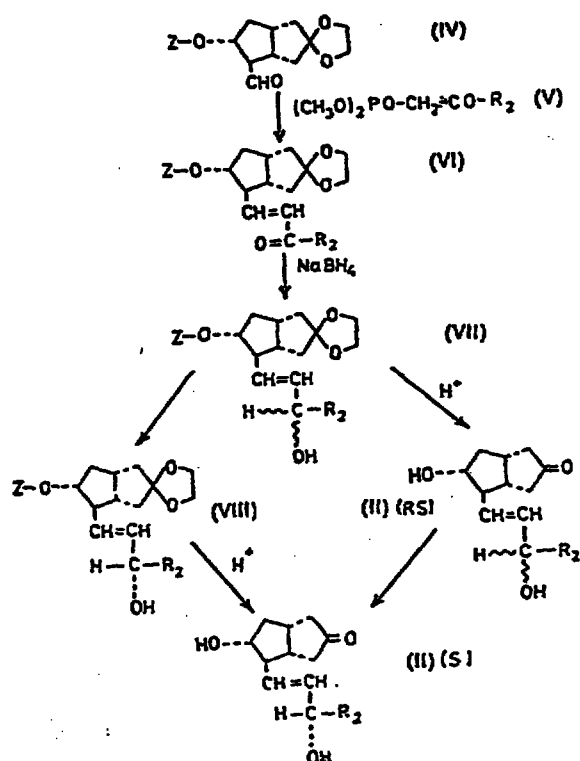
using, for instance, a mixture of methanol/water (80 : 20) as solvent.

The phosphoroalkylenes of the general formula III are obtained by reacting a phosphonium salt of the formula



wherein R_1 has the same meaning as above and Hal is, for example, chlorine or bromine [which salt can be prepared in a manner known per se - c.f. Houben-Weyl "Methoden der organischen Chemie" Vol. 5/4, Stuttgart 1960, page 337 or R.C. Fuson et al., J.Am.Chem.Soc. 62 (1940) page 1180] in the presence of a carefully dried solvent like e.g. benzene, toluene, dimethylsulfoxide, hexamethylphosphoric acid triamide, tetrahydrofuran or the like at a temperature between 0°C and about 100°C , preferably 20°C to 80°C , with a strong base such as potassium tert.-butoxide, methane sulfinyl-sodium, -potassium or -lithium and preferably sodium bis-trimethyl-silylamide. It is not necessary to isolate the compound of formula III from this reaction mixture prior to reacting it with the compound of formula II.

The starting compound of the general formula II, in which R_6 is hydrogen is prepared according to the reaction sequence as outlined schematically in the formulae II(RS), I(S) and IV to VIII (where Z in the formulae given has the same meaning as R_6 with the exception of hydrogen, and R_2 has the same meaning as above):



The following comments are given for further explanation:

The aldehyde IV in which, for instance, Z is a tert.-butyl dimethylsilyl group, i.e. the 3,3-ethylenedioxy-6B-formyl-7 - tert.butyl-dimethylsilyloxy-cis-bicyclo 3.3.0 octane (Nicolaou et al., J.Chem.Soc., Chem. Commun. 1978, 1067) is reacted in a manner known per se with a phosphonate of the general formula V to give a ketone of the general formula VI. The reaction is carried out by carefully excluding humidity and in an inert gas atmosphere such as argon or nitrogen. Suitable solvents are e.g. benzene, toluene, dimethoxyethane, dioxane or tetrahydrofuran. The reaction temperature is between about -20°C and 100°C, preferably between 0°C and 25°C, for about 2 to 24 hours.

The reduction of the resulting keto-compounds VI is carried out by reacting them with a complex boron hydride like sodium borohydride, advantageously with the addition of cerium (III) salts, at a temperature between -40°C and 60°C , preferably between 0°C and 25°C .

The resulting epimeric mixture (VII) may be separated into the S- and R-forms (the latter being without interest in the present invention) by column chromatography on silica gel 60 with a suitable eluant mixture.

The protecting groups, i.e. the ketal group and the tert-butyl dimethylsilyl group, which preferably is the member Z, are split off in an acetic acid containing medium (acetic acid/water/tetrahydrofuran 3 : 1 : 1) at about 25°C c.f. Corey et al., J.Am.Chem.Soc. 94 (1972) 6190; Nicolaou et al., J.Chem.Soc., Chem.Comm. 1978, 1067. Thus the S-Forms of the compounds of formula II are obtained.

It is also possible initially to remove the protecting groups from the epimeric mixture VII and then separate the epimeric mixture of the general formula II (RS) by column chromatography, e.g. on silica gel 60, to obtain the II (S) isomer. To prepare the 3' RS-forms of the compounds of formula I naturally the mixture II (RS) may also be used as starting material which - optionally after introduction of a protecting group R_6 - is reacted with the compound of formula III.

To prepare a compound of formula II in which R_6 is one of the defined protecting groups it is possible to selectively remove the ethylenedioxy group from e.g. a compound of formula VII or VIII. Furthermore it is possible, however, to introduce in the usual manner a protecting group R_6 into a compound of formula II in which R_6 is hydrogen.

The following non-limiting examples serve further to illustrate the invention. In performing them no attempt was made to obtain maximum yields. All temperature references are uncorrected.

The reactions were controlled by thin layer chromatography ("TLC") on plates precoated with silica gel ("Kieselgel 60") of E. Merck.

In column chromatography also silica gel ("Kieselgel 60"), particle size 0.040 - 0.063 mm (230 - 400 mesh ASTM) of Macherey - Nagel was used unless indicated otherwise:

The ratio of the components of the solvent mixtures used in the chromatographic procedures is given in volume/volume.

Ether (which term in the following always means diethyl ether) was distilled before using it in solvent mixtures for column chromatography.

The ^1H -NMR Spectra were measured at 60 MHz, the ^{13}C -NMR-Spectra at 15.08 MHz with the instrument WP-60 of the firm Bruker. The chemical shifts are reported in ppm.

Example 1

a) 3,3-Ethylenedioxy-6 β -(3'-oxo-3'-cyclohexyl-1'E-propenyl)-7-tert.-butyl-dimethylsilyloxy-cis-bicyclo 3.3.0 octane

General formula VI: R_2 = cyclohexyl; Z = tert.-butyl-dimethylsilyl

139 mg of dimethyl 2-oxo-2-cyclohexyl-ethane-phosphonate are dissolved in 2 ml of absolute dimethoxyethane and added dropwise, while stirring at room temperature and in an atmosphere of argon, to a suspension of 28.3 mg dispersed so-

dium hydride (50% dispersion in oil) in 15 ml of absolute dimethoxyethane, and the mixture is stirred for 45 minutes more at room temperature. Thereafter, while stirring at room temperature in an atmosphere of argon, a solution of 194 mg of 3,3-ethylenedioxy-6 β -formyl-7 α -tert.-butyl-dimethylsilyloxy-cis-bicyclo[3.3.0]octane in 1 ml of absolute dimethoxyethane is added dropwise. About 3 hours later a solution of 34.4 μ l of glacial acetic acid in 400 μ l of ether is added and then the mixture is evaporated in a vacuum. The slightly yellowish oily residue is dissolved in 10 ml of ether, washed with 5 ml of a saturated solution of sodium hydrogen carbonate and thereafter with 5 ml of a saturated solution of sodium chloride. After drying over sodium sulfate the solution is evaporated in a vacuum.

The oily residue is purified by column chromatographie using ether/hexane (3 : 2) to give 188 mg (73% of the theoretical yield) of the title compound.



1H -NMR ($CDCl_3$): 6.75 (2d, 1H); 6.15 (d, 1H); 3.93 (s, 4H); 3.89 (s, 1H); 0.95 (s, 9H); 0.8 (s, 6H).

- b) 3,3-Ethylenedioxy-6 β -(3'S-hydroxy-3'-cyclohexyl-1'-E-propenyl)-7 α -tert.-butyl-dimethylsilyloxy-cis-bicyclo-[3.3.0]-octane.

General formula VIII: R_2 = cyclohexyl; Z = tert.-butyl-dimethylsilyl

To a solution of 1.36 g of the compound prepared according to Example 1a in 18 ml of methanol there is added, while stirring and chilling with ice, 7.8 ml of a 0.4 molar solution of cerium-(III)-chloride in methanol followed by the addition in small amounts of 118.5 mg of sodium borohydride.

Thereafter the mixture is stirred for 5 minutes in an ice bath and then for 30 minutes at room temperature whereupon 31 ml of pH7 buffer, 80 ml of dichloromethane and 50 ml of a saturated aqueous solution of potassium sodium tartrate are added, while stirring. The organic layer is separated and the aqueous layer is three times extracted with about 50 ml of dichloromethane each time. The combined dichloromethane solutions are washed with about 25 ml of a saturated solution of sodium chloride, the organic phase is dried over sodium sulfate and then the solution is evaporated in a vacuum.

The oily residue is purified by column chromatography using ether/petroleum ether (1 : 1). Thus 516.2 mg (= 38% of the theoretical yield) of the title compound, 111.4 mg of the corresponding 3'R-isomer and 472.3 mg (35% of the theoretical yield) of the 3'RS-isomeric mixture are obtained, which latter may be further separated by a second chromatography.

$C_{25}H_{44}SiO_4$: 436.718

1H -NMR ($CDCl_3$): 5.48 (m, 2H); 3.90 (s, 4H); 3.76 (m, 2H); 0.91 (s, 9H); 0.6 (s, 6H).

c) 68-(3'S-Hydroxy-3'-cyclohexyl-1'E-propenyl)-7 α -hydroxy-cis-bicyclo[3.3.0]-octane-3-one

General formula II: R_2 = cyclohexyl

516.2 mg of the compound obtained according to Example 1b are stirred for 20 hours at room temperature with 5 ml of a mixture of glacial acetic acid/tetrahydrofuran/water (3 : 1 : 1). (The reaction is controlled by thin layer chromatography using the solvent system ether : acetone = 2 : 1.) After carefully adding 20 ml of a saturated aqueous solution of sodium hydrogen carbonate and of solid sodium hy-

drogen carbonate until the acetic acid is neutralized the mixture is three times extracted with 10 ml of dichloromethane each time. The combined dichloromethane solutions are washed with 10 ml of a saturated solution of sodium chloride, then the organic phase is dried over sodium sulfate and the solution evaporated in a vacuum.

The oily residue is purified by column chromatography (ether/acetone = 2 : 1) to give 301 mg (= 92% of the theoretical yield) of the title compound as a colorless oil which at room temperature slowly solidifies. Melting point: 96 - 97.5°C.

$C_{17}H_{26}O_3$: 278.395

1H -NMR ($CDCl_3$): 5.48 (m, 2H); 2.88 (m, 2H).

^{13}C -NMR (methanol- d_4): 222.52, 134.76, 133.78, 79.01, 78.34, 58.49, 46.63, 45.04, 44.31, 43.52, 42.43, 36.28, 30.01, 27.70, 27.21.

d) 3-(m-Methoxycarbonylbenzylidene)-6β-(3'S-hydroxy-3'-cyclohexyl-1'E-propenyl)-7α-hydroxy-cis-bicyclo[3.3.0]octane.

General formula I: $R_1 = CH_3$; $R_2 = \text{cyclohexyl}$.

To a suspension of 2.141 g of sodium-bis-(trimethylsilyl)-amide in 20 ml of absolute benzene there are added at room temperature with exclusion of humidity and in an atmosphere of nitrogen 5.743 g of m-methoxycarbonyl-benzyl triphenyl phosphoniumbromide, while stirring. The mixture is stirred for 30 minutes at room temperature, heated to gentle boiling under reflux and then allowed to cool to room temperature. After addition of a solution of 224.3 mg of the product obtained in Example 1c in 5 ml of absolute benzene and of

154 μ l of thiophenol the mixture is stirred for one hour at room temperature and then for one week at 50 - 60°C. (TLC solvent: ether/ethyl acetate = 4 : 1)

The reaction mixture is treated with 100 ml of water, the benzene layer is separated and the aqueous layer is extracted three times with 25 ml of ether each time. The combined organic layers are washed with 25 ml of a saturated solution of sodium chloride, dried over sodium sulfate and the solution is evaporated in a vacuum.

The oily residue is purified by column chromatography (ether : ethyl acetate = 4 : 1) to give 145 mg (= 44% of the theoretical yield) of the 3EZ-form of the title compound in form of a colorless oil.

By high performance liquid chromatography under reversed phase conditions column material "LiChrosorb RP 80" 10 μ m (Knauer); column diameter 4.6 mm; flow speed 2 ml/min) the Z- and E-isomers may be separated. Thus 65 mg of the EZ-mixture using methanol : water = 8 : 2 as eluant give 15.6 mg of the Z-isomer and 28.2 of the desired E-isomer of the title compound, which has a melting point of 126.5 - 128°C and gives the following spectral data:

$C_{26}H_{34}O_4$: 410.559

1H -NMR ($CDCl_3$): 7.77 (m, 2H); 7.32 (m, 2H); 6.37 (s broadened, 1H); 5.49 (m, 2H); 3.94 (s, 3H); 3.70 (m, 2H).

^{13}C -NMR (methanol- d_4): 148.39, 140.30, 134.82, 134.33, 134.09, 131.23, 130.31, 129.40, 127.94, 122.58, 78.58, 78.34, 57.76, 52.59, 45.71, 45.04, 42.79, 41.15, 39.87, 38.90, 30.13, 27.70, 27.21.

e) 3EZ-(m-Carboxybenzylidene)-6 β -(3'S-hydroxy-3'-cyclohexyl-

1'E-propenyl)-7 α -hydroxy-cis-bicyclo[3.3.0]octane.

General formula I: R₁ = H; R₂ = cyclohexyl

145 mg of the compound obtained in Example 1d in the EZ-form are dissolved in 5 ml of methanol and treated with 2 ml of 1N sodium hydroxide solution at room temperature for 2 hours, while stirring. (TLC solvent: ether/acetone = 9 : 1). After standing overnight at room temperature 2.2 ml of 1N hydrochloric acid are added, while stirring, followed by extracting three times with 10 ml of dichloromethane each time. The combined dichloromethane solutions are washed with 10 ml of a saturated solution of sodium chloride, dried over sodium sulfate and the solution is evaporated in a vacuum.

Thus 106 mg (= 76% of the theoretical yield) of the title compound are obtained in form of a colorless oil which slowly solidifies on standing at room temperature.

C₂₅H₃₂O₄ : 396.532

¹H-NMR (CDCl₃): 7.85 (m, 2H); 7.37 (m, 2H); 6.33 (s broadened, 1H); 5.46 (m, 2H); 3.67 (m, 2H); 3.08 (s, 3H, replaceable by treatment with D₂O).

- f) This compound may be transformed to its sodium salt (R₁=Na) as follows:

70.2 mg of the carboxy compound are dissolved in 5 ml of methanol and treated with a solution of 29.8 mg of sodium hydrogen carbonate in 3 ml of water, while stirring. After standing overnight the mixture is heated for one hour to 60°C. The solution is evaporated in a vacuum, the residue is triturated with 10 ml of methanol and then again evaporated. The dry residue is three times extracted with 5 ml of methanol each time, the methanolic solution is filtered and

the filtrate is evaporated in a vacuum.

Thus 70.5 mg (= 95% of the theoretical yield) of the sodium salt forming slightly yellowish crystals are obtained.

$C_{25}H_{31}O_4Na$: 418.514

1H -NMR (methanol- d_4): 6.44 (s broadened, 1H); 5.49 (m, 2H).

Example 2

3E-(m-Carboxybenzylidene)-6 β -(3'S-hydroxy-3'-cyclohexyl-1'E-propenyl)-7 α -hydroxy-cis-bicyclo[3.3.0]octane.

General formula I: $R_1 = H$; $R_2 = \text{cyclohexyl}$

Following the procedure described in Example 1e but using 86 mg of the compound obtained in Example 1d (3E-isomer), 12 ml of methanol and 3 ml of 1N sodium hydroxide solution 78,5 mg (95% of the theoretical yield) of the title product are obtained as a colorless oil which solidifies slowly at room temperature. Melting point: 161 - 164°C.

$C_{25}H_{32}O_4$: 396.532

1H -NMR ($CDCl_3$): 7.90 (m, 2H); 7.43 (m, 2H); 6.37 (s broadened, 1H); 5.51 (m, 2H); 3.78 (m, 3H).

Example 3

- a) 3,3-Ethylenedioxy-6 β -(3'-oxo-3'-[1"-adamantyl]-1'E-propenyl)-7 α -tert.butyl-dimethylsilyloxy-cis-bicyclo-[3.3.0]octane.

General formula VI: $R_2 = 1\text{-adamantyl}$; Z = tert.butyl-dimethylsilyl

242.6 mg of a sodium hydride dispersion (50% in oil) in 20 ml of absolute toluene are reacted with 1.47 g of dimethyl 2-oxo-2-(1'-adamantyl)-ethane phosphonate in 40 ml of absolute toluene and with 1.5 g of 3,3-ethylene-dioxy-6 β -formyl-7 α -tert.butyl-dimethylsilyloxy-cis-bicyclo[3.3.0]-octane in 5 ml of absolute toluene in the manner described in Example 1a. The reaction time in this case, is, however, 6 hours, while stirring, followed by storage overnight in an ice box. (TLC solvent: ether : hexane = 1 : 1).

Column chromatography with petroleum ether/ether (4 : 1) yields 999.1 mg (= 45% of the theoretical yield) of the title product.

$C_{29}H_{46}SiO_4$: 486.778

1H -NMR ($CDCl_3$): 6.61 (m, 2H); 3.88 (s, 4H); 3.76 (m, 1H); 0.88 (s, 9H); 0.03 (s, 6H).

The dimethyl 2-oxo-2-(1'-adamantyl)-ethane phosphonate used above was obtained in the following manner:

77.5 ml of a solution of n-butyllithium (15% in hexane) are added dropwise with exclusion of humidity and in an atmosphere of nitrogen to 45 ml of dry ether, while stirring, followed by the addition of 10.8 ml of dimethyl methane phosphonate in 50 ml of dry tetrahydrofuran. After stirring for another 15 minutes period a solution of 10.4 g of ethyl adamantyl-1-carboxylate in 50 ml of dry tetrahydrofuran is added dropwise at $-75^\circ C$, and the mixture is stirred for 3 hours. The temperature is allowed by standing overnight in an ice box to reach $0^\circ C$ and then the pH value of the mixture is adjusted to 4 to 5 by carefully adding 4N hydrochloric acid at $0^\circ C$.

The solution is evaporated in a vacuum, the residue is dissolved in 100 ml of ethyl acetate and washed three times with 30 ml each time of a saturated aqueous solution of sodium chloride. The combined aqueous layers are twice extracted with 10 ml each time of ethyl acetate and then the organic phases are combined, dried over sodium sulfate and the solution is evaporated in a vacuum. The oily residue is distilled in a vacuum to give 10.4 g (72% of the theoretical yield) of the product in form of a colorless oil boiling at 0.2 mm Hg and 170 - 171°C.

$^1\text{H-NMR}$ (CDCl_3): 3.86 (s, 3H); 3.67 (s, 3H); 3.31 (s, 1H); 2.96 (s, 1H); 1.94 (m, 15H).

- b) 3,3-Ethylenedioxy-6 β -(3'S-hydroxy-3'-[1"-adamantyl]-1'E-propenyl)-7 -tert.butyl-dimethylsilyloxy-cis-bicyclo[3.3.0]-octane.

General formula VIII: $\text{R}_2 = 1\text{-adamantyl}$; $\text{Z} = \text{tert.butyl-dimethylsilyl}$

In analogy to Example 1b there are reacted 422.5 mg of the product obtained in Example 3a, dissolved in 5 ml of methanol, 2.6 ml of 0.4 molar solution of cerium-(III)-chloride in methanol and 51.3 mg of sodium borohydride to give after column chromatography with petrolether/ether (2 : 1) 314.1 mg (= 74% of the theoretical yield) of the title compound and 56.9 mg of the 3'R-isomer, which is discarded.

$\text{C}_{29}\text{H}_{48}\text{SiO}_4$: 488.794

3'S-isomer:

$^1\text{H-NMR}$ (CDCl_3): 5.50 (m, 2H); 3.93 (s, 4H); 3.70 (m, 2H); 0.93 (s, 9H); 0.08 (s, 6H).

^{13}C -NMR (methanol- d_4): 134.88, 130.37, 119.97, 82.05, 80.28, 65.37, 64.76, 58.07, 43.95, 43.10, 42.49, 40.91, 39.26, 38.29, 37.80, 36.77, 29.58, 26.48, 18.81.

- c) 6B-(3'S-Hydroxy-3'-[1"-adamantyl]-1'E-propenyl)-7 α -hydroxy-cis-bicyclo[3.3.0]-octane-3-one.

General formula II: $R_2 = 1\text{-adamantyl}$

In analogy to Example 1c, there are obtained from 314.1 mg of the product of Example 3b after column chromatography with ether/acetone (3 : 1) 192.2 mg of the title compound in form of white crystals. Melting point: 142 - 143.5°C (after recrystallization from diisopropylether).

$\text{C}_{21}\text{H}_{30}\text{O}_3$: 330.471

^1H -NMR (CDCl_3): 5.52 (m, 2H); 3.95 (m, 1H); 3.53 (m, 1H).

- d) 3EZ-(m-Methoxycarbonylbenzylidene)-6B-(3'S-hydroxy-3-[1"-adamantyl]-1'E-propenyl)-7 α -hydroxy-cis-bicyclo[3.3.0]octane.

General formula I: $R_1 = \text{CH}_3$; $R_2 = 1\text{-adamantyl}$

In analogy to Example 1d there are reacted 195.9 g of m-methoxycarbonylbenzyl triphenyl phosphonium-bromide and 1.09 g of sodium-bis-trimethylsilyl-amide. After column chromatography with ether/acetone (4 : 1) 114.4 mg (= 42% of the theoretical yield) of the title compound in solid form are obtained.

$\text{C}_{30}\text{H}_{38}\text{O}_4$: 462.636

^1H -NMR (CDCl_3): 7.86 (m, 2H); 7.36 (m, 2H); 6.35 (s broadened, 1H); 5.50 (m, 2H); 3.88 (s, 3H); 3.80 (m, 2H).

- e) 3EZ-(m-Carboxybenzylidene)-6B-(3'S-hydroxy-3'-[1"-adamantyl]-1'E-propenyl)-7 α -hydroxy-cis-bicyclo[3.3.0]octane.

General formula I: $R_1 = H$; $R_2 = 1\text{-adamantyl}$

In analogy to Example 1e from 110.4 mg of the product prepared in Example 3d, dissolved in 10 ml of methanol, with 3 ml of 1N sodium hydroxide solution 79.3 mg of the title compound (= 74% of the theoretical yield) are obtained in solid form.

$C_{29}H_{36}O_4$: 448.609

1H -NMR ($CDCl_3$): 7.83 (m, 2H); 7.37 (m, 2H); 6.37 (s broadened, 1H); 5.48 (m, 2H); 3.47 (m, 2H); 3.25 (s, 3H, replaceable by treatment with D_2O).

Example 4

By using the appropriate reactants and otherwise proceeding as described in Examples 1 to 3, there are obtained:

- a) 3E-(m-Ethoxycarbonyl-benzylidene)-6B-(3'S-hydroxy-3'-cyclohexyl-1'E-propenyl)-7 α -hydroxy-cis-bicyclo[3.3.0]octane.

General formula I: $R_1 = C_2H_5$; $R_2 = \text{cyclohexyl}$

$C_{27}H_{36}O_4$: 424.586

Melting point: 115 - 116°C

1H -NMR ($CDCl_3$): 7.78 (m, 2H); 7.30 (m, 2H); 6.31 (s broadened, 1H); 5.48 (m, 2H); 4.23 (q, 2H); 3.70 (m, 2H); 1.38 (t).

- b) 3E(m-[n-Propyloxycarbonyl]-benzylidene)-6B-(3'S-hydroxy-3'-cyclohexyl-1'E-propenyl)-7 α -hydroxy-cis-bicyclo[3.3.0]octane.

General formula I: $R_1 = n\text{-C}_3\text{H}_7$; $R_2 = \text{cyclohexyl}$

$\text{C}_{28}\text{H}_{38}\text{O}_4$: 438.613

Melting point: 68 - 71°C

$^1\text{H-NMR}$ (CDCl_3): 7.78 (m, 2H); 7.32 (m, 2H); 6.33 (s broadened, 1H); 5.43 (m, 2H); 4.23 (t, 2H); 3.64 (m, 2H).

- c) Sodium salt of 3E-(m-carboxybenzylidene)-6 β -(3'S-hydroxy-3'-cyclohexyl-1'E-propenyl)-7 α -hydroxy-cis-bicyclo[3.3.0]octane.

General formula I: $R_1 = \text{Na}$; $R_2 = \text{cyclohexyl}$

$\text{C}_{25}\text{H}_{31}\text{O}_4\text{Na}$: 418.514

$^1\text{H-NMR}$ (methanol- d_4): 6.44 (s broadened, 1H); 5.51 (m, 2H):

- d) 3E-(m-Carboxybenzylidene)-6 β -(3'S-hydroxy-3'-[adamantyl-1"]-1'E-propenyl)-7 α -hydroxy-cis-bicyclo[3.3.0]octane.

General formula I: $R_1 = \text{H}$; $R_2 = \text{adamantyl}$

$\text{C}_{29}\text{H}_{36}\text{O}_4$: 448.609

$^1\text{H-NMR}$ (methanol d_4): 7.78 (m, 2H); 7.37 (m, 2H); 6.38 (s broadened, 1H); 5.50 (m, 2H).

- e) 3ZE-(m-Carboxybenzylidene)-6 β -(3'S-hydroxy-3'-[3",5"-dimethyladamantyl-1"]-1'E-propenyl)-7 α -hydroxy-cis-bicyclo[3.3.0]octane.

General formula I: $R_1 = \text{H}$; $R_2 = 3,5\text{-dimethyladamantyl-1}$

- f) 3E-(m-[tert.-Butyloxycarbonyl]-benzylidene)-6 β -(3'S-hydroxy-

3'-cyclohexyl-1'E-propenyl)-7 α -hydroxy-cis-bicyclo[3.3.0]-octane.

General formula I: $R_1 = (CH_3)_3C-$; $R_2 = \text{cyclohexyl}$

g) 3E-(m-Carboxybenzylidene)-6 β -(3'S-hydroxy-3'-[4"-methyl-cyclohexyl]-1'E-propenyl)-7 α -hydroxy-cis-bicyclo[3.3.0]octane.

General formula I: $R_1 = H$; $R_2 = 4\text{-methylcyclohexyl}$

h) Potassium salt of 3E-(m-carboxybenzylidene)-6 β -(3'S-hydroxy-3'-cyclohexyl-1'E-propenyl)-7 α -hydroxy-cis-bicyclo[3.3.0]-octane.

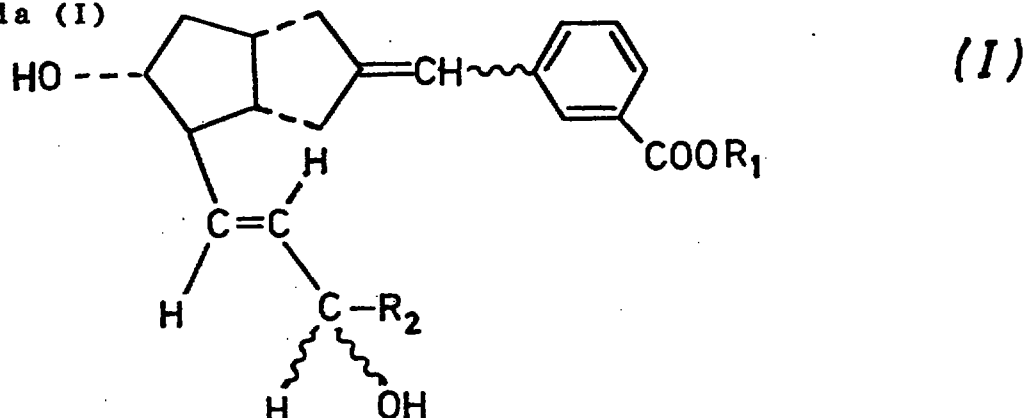
General formula I: $R_1 = K$; $R_2 = \text{cyclohexyl}$

and other compounds of formula I.



Claims

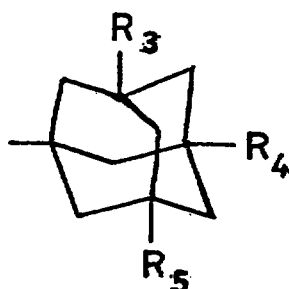
1. New cis-bicyclo-[3.3.0]-octane derivatives corresponding to the Formula (I)



in which the phenyl radical may have the EZ- or Z-configuration in relation to the double bond whilst the RS- or S-configuration may be present on the carbon atom carrying the radical R_2 and in which

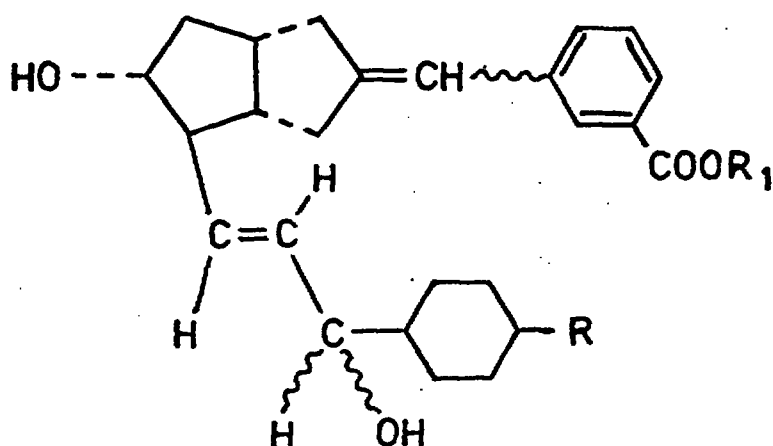
R_1 represents a hydrogen atom, a straight-chain or branched alkyl radical containing from 1 to 4 carbon atoms or a pharmaceutically acceptable cation, and

R_2 represents a cyclohexyl radical, a 4-methylcyclohexyl radical or a 1-adamantyl radical having the following structure



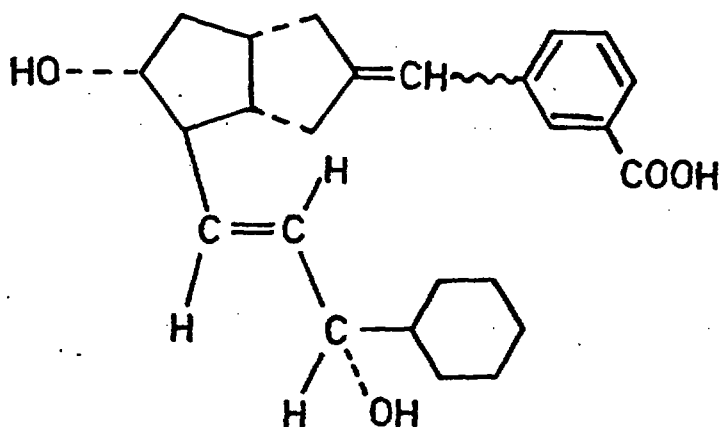
in which R_3 , R_4 and R_5 may be the same or different and represent hydrogen or methyl.

2. New cis-bicyclo-[3.3.0]-octane derivatives corresponding to the following formula



in which R_1 has the same meaning as in Formula (I), R represents hydrogen or methyl, and in which the phenyl radical may have the EZ- or E-configuration in relation to the double bond whilst the 3'RS- or S-configuration may be present on the carbon atom attached to the cyclohexyl radical.

3. New cis-bicyclo-[3.3.0]-octane derivatives as claimed in Claims 1 and 2 in which R_1 represents a methyl or an ethyl radical.
4. New cis-bicyclo-[3.3.0]-octane derivatives as claimed in Claims 1 and 2 in which R_1 represents a sodium or a potassium ion.
5. The 3'S-forms of the new cis-bicyclo-[3.3.0]-octane derivatives claimed in Claims 1 to 4.
6. 3-(m-Carboxybenzylidene)-6 β -(3'S-hydroxy-3'-cyclohexyl-1'E-propenyl)-7 α -hydroxy-cis-bicyclo-[3.3.0]-octane corresponding to the following formula



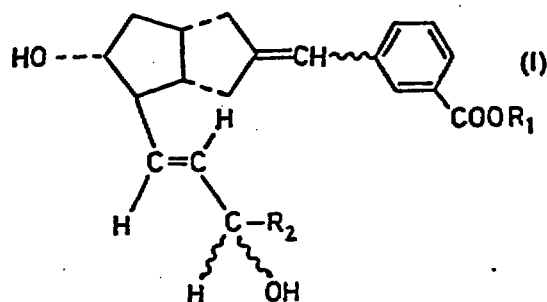


in the 3EZ- or 3E-configuration and its pharmaceutically acceptable salts, particularly its sodium salt.

7. A medicament, characterized in that it contains as active principle at least one cis-bicyclo-[3.3.0]-octane derivative of the type claimed in Claims 1 to 6.
8. A medicament as claimed in Claim 7, characterized in that it contains as active principle from 0.01 to 50 mg per single dose of a cis-bicyclo-[3.3.0]-octane derivative of the type claimed in Claims 1 to 6.
9. A medicament as claimed in Claims 7 and 8, characterized in that it is suitable for parenteral application and contains from 0.01 to 10 mg of a cis-bicyclo-[3.3.0]-octane derivate of the type claimed in Claims 1 to 6.
10. A medicament as claimed in Claim 9 for parenteral application, characterized in that it contains from 0.01 to 10 mg of a cis-bicyclo-[3.3.0]-octane derivative of the type claimed in Claims 1 to 6 in dissolved or suspended form in a liquid, sterile vehicle.
11. A medicament as claimed in Claims 8 and 9, characterized in that it is suitable for oral application and contains from 0.1 to to 50 mg of a cis-bicyclo-[3.3.0]-octane derivative of the type claimed in Claims 1 to 6.
12. A medicament as claimed in Claim 11 for oral application, characterized in that it is in the form of tablets, dragees or capsules.
13. A medicament as claimed in Claim 7, characterized in that it is in the form of sustained-release tablets, dragees or capsules and contains up to 250 mg per individual dose of a cis-bicyclo-[3.3.0]-octane derivative of the type claimed in Claims 1 to 6.



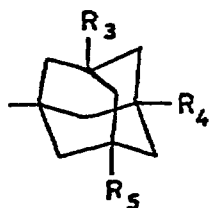
14. A process for the production of new cis-bicyclo-[3.3.0]-octane derivatives corresponding to the Formula (I)



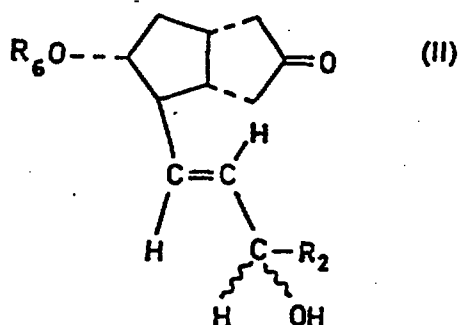
in which the phenyl radical may have the EZ- or E-configuration in relation to the double bond whilst the RS- or S-configuration may be present on the carbon atom carrying the radical R_2 , and in which

R_1 represents a hydrogen atom, a straight-chain or branched alkyl radical containing from 1 to 4 carbon atoms or a pharmaceutically acceptable cation, and

R_2 represents a cyclohexyl radical, a 4-methylcyclohexyl radical or a 1-adamantyl radical having the following structure



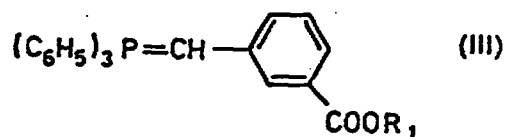
in which R_3 , R_4 and R_5 may be the same or different and represent hydrogen or methyl, characterized in that a compound corresponding to the general Formula (II)





in which R_2 is as defined above and R_6 represents a hydrogen atom or a protective group which can be eliminated under mild conditions,

is reacted at about 0 to about 100°C with a compound corresponding to the Formula (III)



in which R_1 is as defined above,
in the presence of aprotic solvents and in the absence of moisture and oxygen and, where R_6 is different from hydrogen, the protective group R_6 is subsequently eliminated.

15. A process as claimed in Claim 14, characterized in that the reaction is carried out in the presence of a weakly acidic compound, more particularly an optionally substituted thiophenol.
16. A process as claimed in Claims 14 and 15, characterized in that in the compound obtained corresponding to Formula (I), when R_1 therein is an alkyl radical, the group COOR_1 is hydrolyzed to form the carboxyl group and the product thus obtained (with $R_1 = \text{H}$) is then optionally converted into a pharmaceutically acceptable salt.
17. A process for producing the medicaments claimed in Claims 7 to 13, characterized in that the cis-bicyclo-[3.3.0]-octane derivatives claimed in Claims 1 to 6 are processed in the usual way with carrier materials, diluents and, optionally, binders, tablet disintegrating agents and other standard auxiliaries and the individual dosage forms are prepared from the mixture obtained.