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(54) Title
USE OF PHOSPHORUS DERIVATIVES OF ALKALOIDS FOR TREATING ENDOCRINOPATHIES

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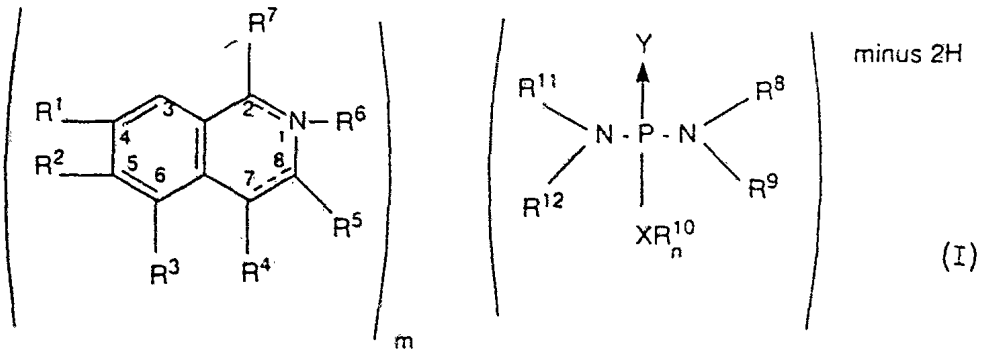
(57) Claim

1. A method of treatment of endocrinopathies involving administration to a patient in need thereof, a therapeutically effective amount of phosphorus derivatives of alkaloids of the general formula (I)



(I)

wherein m and n = 1, 2 or 3; R^1, R^2 and R^3 independently each represent H or methoxy, wherein R^1 and R^2 or R^2 and R^3 together also may represent a methylene dioxy group; Y = O or S; X = O or N.

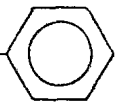
R^4 and R^5 together with the C atoms to which they are attached form a possibly totally or partially hydrogenated phenyl or naphthyl group, which in turn may be substituted by methoxy, hydroxy or dioxymethyl, and R^7 is H or =O or an ring system defined above bonded via a $-CH_2-CO-CH_2-$ chain, R^6 is $-CH_3$ and double bonds may be present in positions 1, 2 and/or 7, 8; or

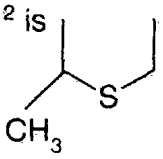
.../2

R^6 and R^7 together with the C and N atom to which they are attached form a possibly hydrogenated benzo or naphtho ring system, which contains one N-Atom and which in turn may be substituted by methoxy, oxo, methyl or dioxy-methyl groups, and R^4 and R^5 represent H;

R^{10} = 2H, $-CH_2-CH_2-$, H or $-CH_2-CH_2Cl$;

$R^8 + R^9$ together and $R^{11} + R^{12}$ together are $-CH_2-CH_2-$ and, if Y = S, X = N and n = 2, R^{11} and R^{12} together represent $-CH_2-CH_2-$, $-CH_2-CH_2-O-CH_2-CH_2-$ or $-CH_2-CH_2-N(CH_3)-CH_2-CH_2-$; or if

Y = O, X = N, n = 1, R^{12} is  ;

Y = O, X = N, n = 2, R^{11} and R^{12} is  ; and if

Y = O, X = O, n = 1;

R^8 and R^9 are each $-CH_2-CH_2-Cl$, R^{10} is H and $R^{11} + R^{12}$ together are $-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-$, as well as the salts thereof with pharmaceutically compatible acids.

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(54) Title: USE OF PHOSPHORUS DERIVATIVES OF ALKALOIDS FOR TREATING ENDOCRINOPATHIES

(54) Bezeichnung: VERWENDUNG VON PHOSPHORDERIVATEN VON ALKALOIDEN ZUR BEHANDLUNG VON ENDOKRINOPATHIEN

(57) Abstract

The invention concerns the use of phosphorus derivatives of alkaloids of the general formula (I), as disclosed in AT-PS 377 988 and AT-PS 354 644, for preparing a medicament for treating endocrinopathies, in particular for treating osteoporosis.

(57) Zusammenfassung

Beschrieben wird die Verwendung von Phosphorderivaten von Alkaloiden der allgemeinen Formel (I), wie sie in der AT-PS 377 988 bzw. in der AT-PS 354 644 geoffenbart werden, zur Herstellung eines Arzneimittels zur Behandlung von Endokrinopathien, insbesondere zur Behandlung von Osteoporose.

USE OF PHOSPHORUS DERIVATIVES OF ALKALOIDS FOR TREATING ENDOCRINOPATHIES

The present invention relates to the use of phosphorus derivatives of alkaloids for producing a medicament for treating endocrinopathies.

The term endocrinopathies indicates syndromes in which dyshormonisms are the main cause and determinative of the disease. The causes of such syndromes may reside in diseases of the endocrinal glands, e.g. in an increased hormone production or in a hormome hunger or in a complete absence of hormones, in dysfunctions of the endocrinal glands due to regulatory processes, in derailed hormone formation as a consequence of pathological enzyme systems or in a changed responsiveness of various organs to hormones.

Osteoporosis also can be counted among the endocrinopathies, this being the quantitative reduction of the bone tissue with a retained bone structure due to an increased bone degradation and/or a reduced bone formation, accompanied by the increased occurrence of heparin-containing mast cells in the bone marrow. The etiology of this disease is largely unclear, yet there are strong hints indicating that it is at least very much encouraged by an estrogen deficiency due to the incidence of menopause.

An article by H. Resch et al. (Calcif. Tissue Int. (1989) 45:209-213) proposes the combined administration of calcitonin and a cyclical hormone replacement therapy for the treatment of osteoporosis. Furthermore, in Acta Endocrinologica 1990, 123, p. 14-18, the same author has described the cyclical estrogen/progestogen replacement therapies for treating osteoporosis. The results of these studies indicate that hormone treatment of patients suffering from osteoporosis seems to be promising.

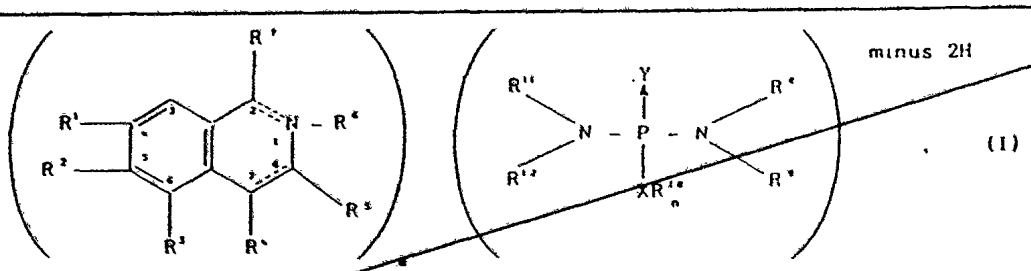
In Osteoporosis, Wilhelm Maudrich Publishers, Wien-München-Bern, 1989, B.E.C. Nordin also argues that at least in women the increased bone resorption involved with osteoporosis presumably goes back to a decreasing functioning of the ovaries, the androstenedione produced by the suprarenal cortex being the only estrogen source after menopause, from which in turn only slight amounts of estradiole are being produced. A small amount of

estradiol is formed by the peripheral conversion from testosteron, which in turn is partly formed from the androstenedione of the suprarenal cortex and partly is formed in the post-menopausal ovary. In view of this rather complex mechanism, it is hard to say which hormonal changes are responsible for the increasing bone resorption in menopause. Since the latter is reversible by an estrogen therapy, it is probably due to the decrease of the entire effective estrogen activity (estradiol and estrone). However, the ovary insufficiency need not necessarily have a direct effect on the bones; indirectly it would act via changes in the calcitonin secretion. In the direct post-menopausal phase, the serum calcium and the urine calcium certainly will increase without an increase in the calcium resorption, and in this case the calcium demand may even rise to up to 35 mmol/day. As regards the effects of various hormones or the deficiencies thereof, respectively, on osteoporosis, reference is made to the last-mentioned publication by B.E.C. Nordin.

AT PS 377 988 and AT PS 354 644 disclose methods of producing novel phosphorus derivatives of alkaloides and novel salts of alkaloid derivatives of thiophosphoric acid, respectively. Such compounds have a pharmacological activity and may be used as cytostatic agents.

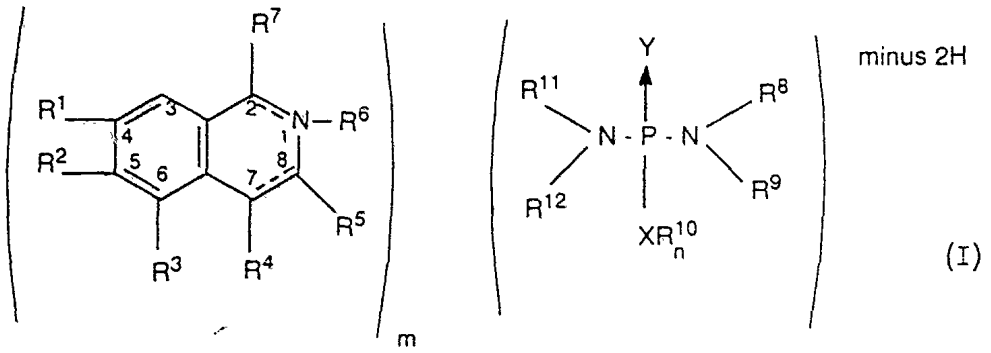
Surprisingly it has now been found that the phosphorus derivatives of alkaloids disclosed in AT PS 377 988 and AT PS 354 644, respectively, can be used for the production of medicaments for the treatment of endocrinopathies, in particular for the treatment of osteoporosis.

Methods of producing phosphorus derivatives of alkaloids of the general formula (I)



(I)

wherein m and n = 1, 2 or 3; R^1, R^2 and R^3 are each independently H or methoxy, wherein R^1 and R^2 or R^2 and R^3



(I)

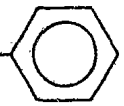
wherein m and n = 1, 2 or 3; R^1, R^2 and R^3 independently each represent H or methoxy, wherein R^1 and R^2 or R^2 and R^3 together also may represent a methylene dioxy group; Y = O or S; X = O or N.

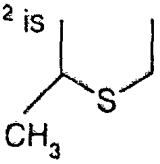
R^4 and R^5 together with the C atoms to which they are attached form a possibly totally or partially hydrogenated phenyl or naphthyl group, which in turn may be substituted by methoxy, hydroxy or dioxymethyl, and R^7 is H or =O or an ring system defined above bonded via a $-CH_2-CO-CH_2-$ chain, R^6 is $-CH_3$ and double bonds may be present in positions 1, 2 and/or 7, 8; or

R^6 and R^7 together with the C and N atom to which they are attached form a possibly hydrogenated benzo or naphtho ring system, which contains one N-Atom and which in turn may be substituted by methoxy, oxo, methyl or dioxy-methyl groups, and R^4 and R^5 represent H;

R^{10} = 2H, $-CH_2-CH_2-$, H or $-CH_2-CH_2Cl$;

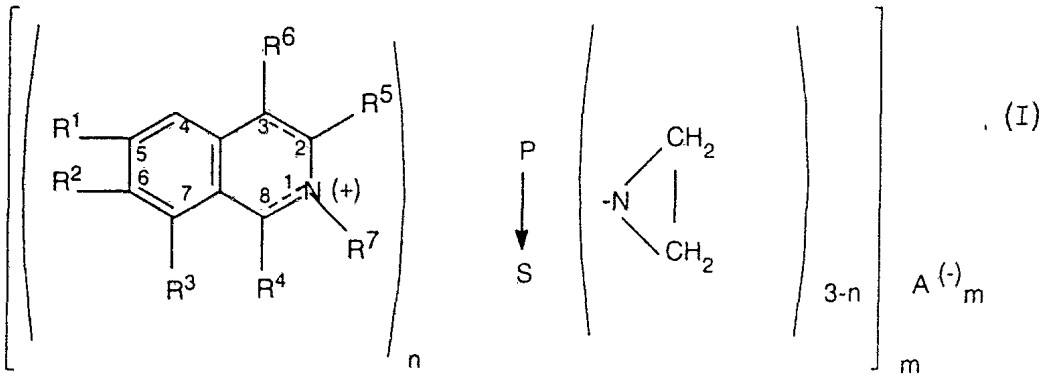
$R^8 + R^9$ together and $R^{11} + R^{12}$ together are $-CH_2-CH_2-$ and, if Y = S, X = N and n = 2, R^{11} and R^{12} together represent $-CH_2-CH_2-$, $-CH_2-CH_2-O-CH_2-CH_2-$ or $-CH_2-CH_2-N(CH_3)-CH_2-CH_2-$; or if

Y = O, X = N, n = 1, R^{12} is  ;

Y = O, X = N, n = 2, R^{11} and R^{12} is  ; and if

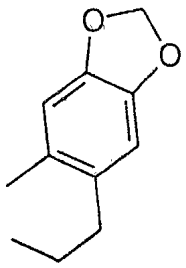
Y = O, X = O, n = 1;

R^8 and R^9 are each $-CH_2-CH_2-Cl$, R^{10} is H and R^{11} + R^{12} together are $-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-$, as well as the salts thereof with pharmaceutically compatible acids, are known from AT PS 377 988; the preparation of alkaloid derivatives of thiophosphoric acid of the general formula



(I)

wherein n is 1, 2 or 3; m is 1, 2 or 3; R^1, R^2 and R^3 independently each are hydrogen or methoxy, wherein R^1 and R^2 together or R^2 and R^3 together also may represent a methylenedioxy group; R^4 is hydrogen, hydroxy or methyl; and, if R^7 is hydrogen, R^5 and R^6 together form the group



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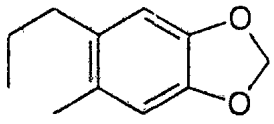
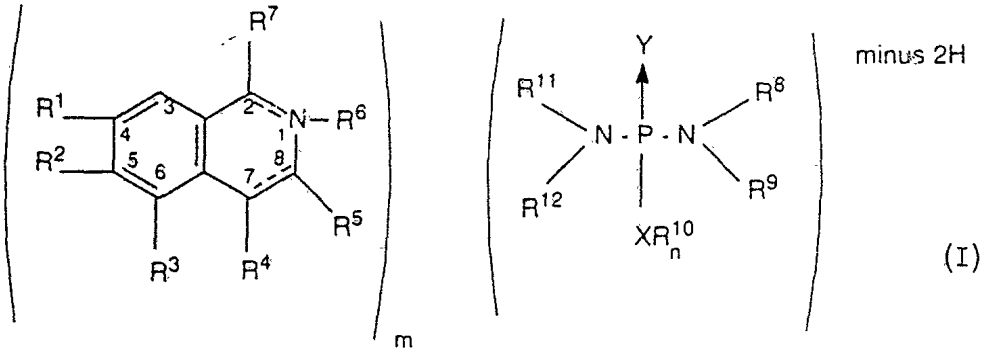
or, if R^7 is a methyl group, the groups R^5 and R^6 represent the group



;

and in positions 1, 8 and/or 2, 3 a double bond may be present; and A is a monovalent or the equivalent portion of a polyvalent anion, is disclosed in AT PS 354 644.

In one embodiment the present invention provides a method of treatment of endocrinopathies involving administering to a patient in need thereof, a pharmaceutically effective amount of phosphorus derivatives of alkaloids of the general formula (I)



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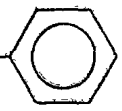
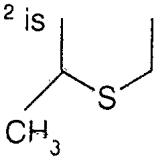
Y = O, X = N, n = 1, R^{12} is -CO-  ;

Y = O, X = N, n = 2, R^{11} and R^{12} is  ; and if

Y = O, X = O, n = 1;

R^8 and R^9 are each $-CH_2-CH_2-Cl$, R^{10} is H and R^{11} + R^{12} together are $-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-$, as well as the salts thereof with pharmaceutically compatible acids, and optionally, a pharmaceutically acceptable carrier.

According to a particularly preferred embodiment of the present invention, the reaction product of the alkaloids of chelidonium majus L. with thiophosphoric acid triaziridide is used for the production of a medicament for the treatment of endocrinopathies, in particular for the treatment of osteoporosis. For reasons of simplicity, this reaction product will be termed "ukrain" in the following.

The surprising effect of ukrain in the treatment of endocrinopathies shall be demonstrated in the following by way of an animal test model.

Therein, the sustained action of ukrain on some biochemical and biomechanical parameter is investigated in ovariectomized rats.

Ovariectomy is an acknowledged model for the experimental osteoporosis. The test animals received intraperitoneal injections of ukrain at a dose of 28 mg/kg body weight per day for 6 months, starting from the second day after the removal of the ovaries or after corresponding surgery without removal of the ovaries (control group with surgical shock). Ovariectomy caused changes in the peripheral blood morphology, the activity of amino transferases (ALT and AST) and in the total serum protein level as well as in the serum hormone concentrations and in the amount of catecholamines in the complete brains of the rats. The changes are given in detail in the following tables.

T A B L E I

Effects of the 6-month treatment with ukrain on the levels of some hormones in the sera of ovariectomized rats (N = 10)

Treatment	Prolactin ng/ml	Progesterone ng/ml	ACTH pg/ml	Corticosterone ng/ml	Aldosterone pg/ml	T-3 ng/ml	T-4 ng/ml	T_3-Uptake %
Control group	18.5±0.02	12.9±2.9	115.6±26.36	470±79.7	227.14±30.5	0.82±0.07	140.8±5.2	41.7±1.09
Control group with surgical shock	10.5±0.15	17.9±5.8	167.85±66.25	513.12±112.2	361.2±89.2	0.72±0.14	141.2±9.3	41.4±0.98
Ovariectomized control group	9.3±0.16	5.56±1.38	99.37±21.2	434.0±83.9	246±40.9	0.52±0.036	140.5±6.3	41.98±0.41
Ovariectomy, treatment with ukrain 28 mg/kg body weight i.p.	11.9±0.01	20.9±0.49	114.6±20.9	243.7±46.1	97.8±30.9	0.49±0.03	130.4±9.7	41.37±0.67

T3 = Triiodothyroidine T4 = Thyroxine

TABLE II

Effects of the 6-month-treatment with ukrain on the amounts of noradrenaline (NA) and dopamine (DA) in the complete brains in ovariectomized rats (N = 10)

Treatment	ng/g Fresh Tissue	
	NA	DA
Control group	1.214 ± 0.043	0.778 ± 0.032
Control group with surgical shock	1.4703 ± 0.077	0.913 ± 0.061
Ovariectomized control group	1.625 ± 0.064	1.0208 ± 0.047
Ovariectomy, treatment with ukrain 28 mg/kg body weight, i.p.	1.274 ± 0.085	0.920 ± 0.027

TABLE III

Effects of the 6-month-treatment with ukrain on the activities of aminotransferases (ALT and AST) in the sera of ovariectomized rats (N = 10)

Treatment	Activity, i.p.	
	ALT	AST
Control group	25.3 ± 0.4	19 ± 0.6
Control group with surgical shock	25.8 ± 0.4	23.5 ± 0.5
Ovariectomized control group	25.1 ± 0.6	21.3 ± 0.3
Ovariectomy, treatment with ukrain 28 mg/kg body weight, i.p.	24 ± 0.4	19.4 ± 0.3

TABLE IV

Effects of 6-month-treatment with ukrain on the peripheral blood morphologies in overiectomized rats (N = 10)

Treatment	Hemoglobin g %	Erythrocytes $10^6/mm^3$	Haematocrit %	Leucocytes $10^3/mm^3$
Control group	14.4 ± 0.14	7.5 ± 0.08	40.8 ± 0.3	14.4 ± 0.14
Control group with surgical shock	15.5 ± 0.2	8.18 ± 0.06	45.6 ± 0.17	15.5 ± 0.2
Ovariecto-mized control group	15.5 ± 0.3	8.05 ± 0.02	44.9 ± 0.04	15.5 ± 0.3
Ovariectomy, treatment with ukrain 28 mg/kg body weight i.p.	14.8 ± 0.07	7.9 ± 0.03	43.2 ± 0.2	14.8 ± 0.07

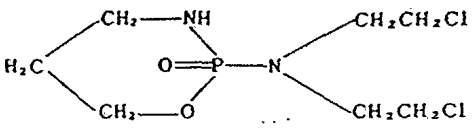
From the above Tables I to IV it is apparent that the changes caused by ukrain in ovariectomized rats is significant insofar as all the parameters which are out of the ordinary after an ovariectomy and thus, most likely, also in case of osteoporosis, are improved.

In this context it is also particularly remarkable that after the treatment and sacrifice of the animals a significantly better mechanical breaking loadability of the femora resulted in animals treated with ukrain as compared to the ovariectomized control group.

As the alkaloid component, the following have proved particularly suitable: Coptisin, stylopin, berberin, protopin allo-cryptopin, spartein, corysamin, chelidimerin, oxysanguinarin, sanguinarin, dihydroxysanguinarin, chelidonin,

homochelidonin, methoxy-chelidonin, chelerythrin, chelilutin, winblastin, colchicin, cholchicein, desacetyl-N-methyl-colchicin.

As the phosphorus compound for the reaction, the following are particularly suitable:



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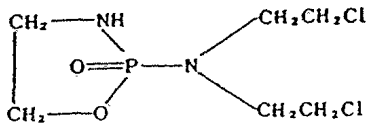

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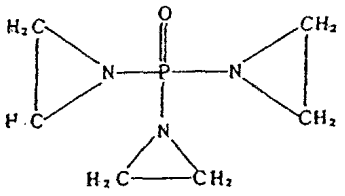

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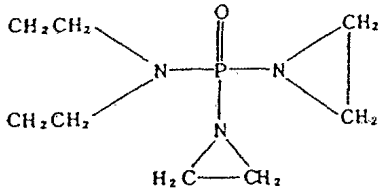

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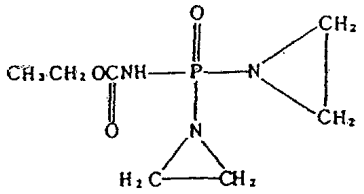

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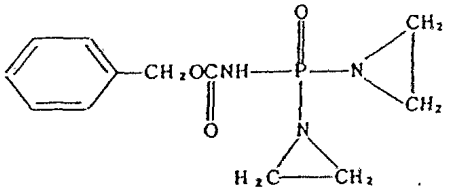

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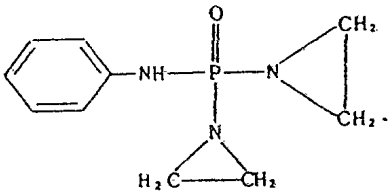
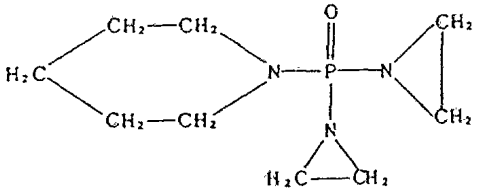


(LVIII)



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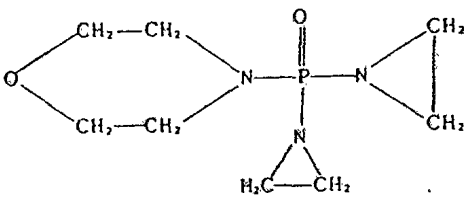
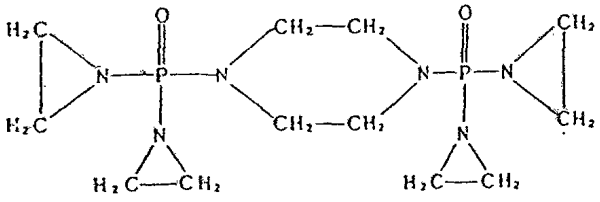


(LX)



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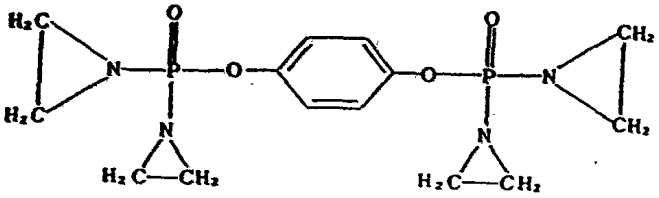

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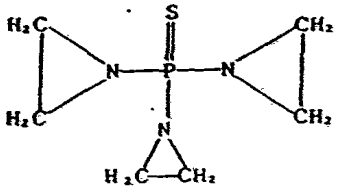

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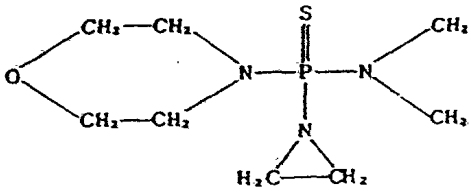

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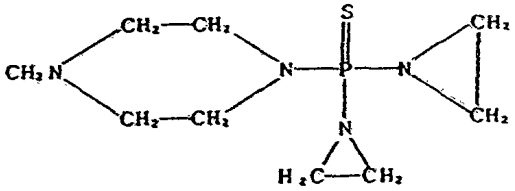
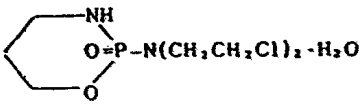
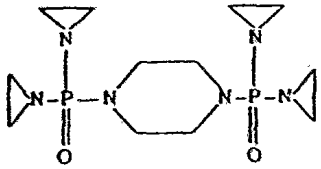
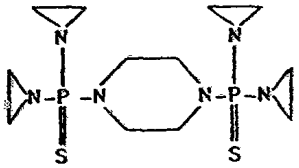
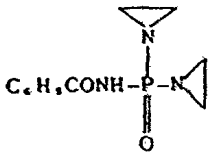


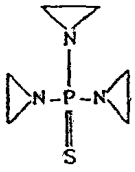
(LXV)

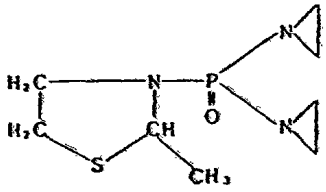


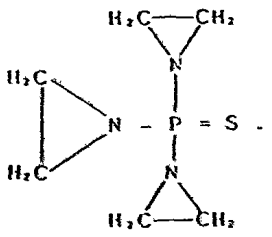










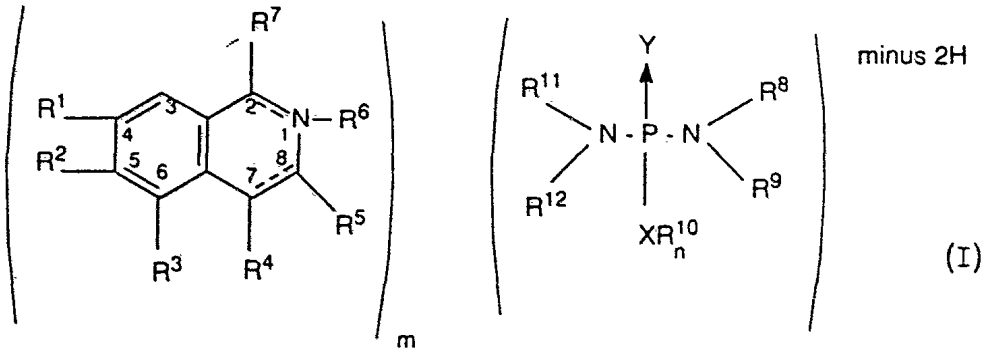


The medicaments produced according to the invention preferably are comprised of an aqueous solution of the alkaloid phosphorus derivatives used or of the salts thereof, possibly in combination with further auxiliary agents known *per se*. The medicament according to the invention preferably is administered by way of injection, e.g. intraperitoneally, intramuscularly or intravenously, the dosage being dependent on the respective case and on the severity of the disease to be treated as well as on the condition of the patient.

It is within the knowledge of the medical doctor in charge to determine the suitable dosage in each case.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of treatment of endocrinopathies involving administration to a patient in need thereof, a therapeutically effective amount of phosphorus derivatives of alkaloids of the general formula (I)



(I)

wherein m and n = 1, 2 or 3; R^1, R^2 and R^3 independently each represent H or methoxy, wherein R^1 and R^2 or R^2 and R^3 together also may represent a methylene dioxy group; Y = O or S; X = O or N.

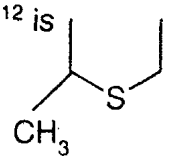
R^4 and R^5 together with the C atoms to which they are attached form a possibly totally or partially hydrogenated phenyl or naphthyl group, which in turn may be substituted by methoxy, hydroxy or dioxymethyl, and R^7 is H or =O or an ring system defined above bonded via a $-CH_2-CO-CH_2-$ chain, R^6 is $-CH_3$ and double bonds may be present in positions 1, 2 and/or 7, 8; or

R^6 and R^7 together with the C and N atom to which they are attached form a possibly hydrogenated benzo or naphtho ring system, which contains one N-Atom and which in turn may be substituted by methoxy, oxo, methyl or dioxy-methyl groups, and R^4 and R^5 represent H;

R^{10} = 2H, $-CH_2-CH_2-$, H or $-CH_2-CH_2Cl$;

$R^8 + R^9$ together and $R^{11} + R^{12}$ together are $-CH_2-CH_2-$ and, if Y = S, X = N and n = 2, R^{11} and R^{12} together represent $-CH_2-CH_2-$, $-CH_2-CH_2-O-CH_2-CH_2-$ or $-CH_2-CH_2-N(CH_3)-CH_2-CH_2-$; or if

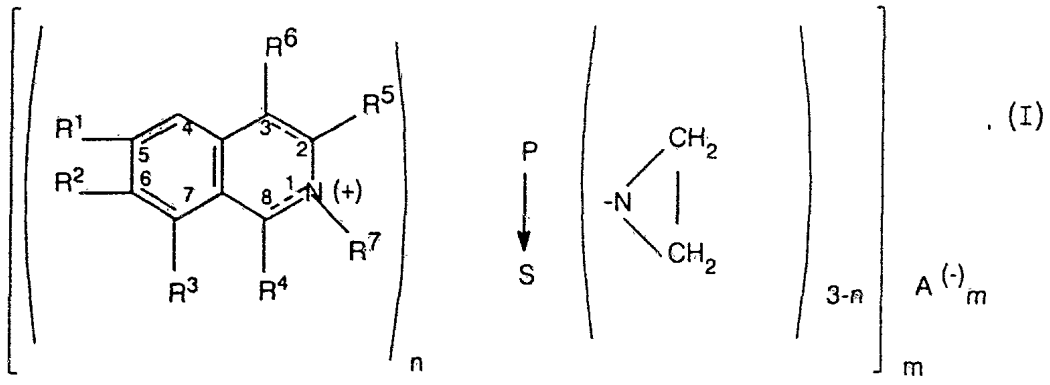
Y = O, X = N, n = 1, R^{12} is -CO-  ;

Y = O, X = N, n = 2, R^{11} and R^{12} is  ; and if

Y = O, X = O, n = 1;

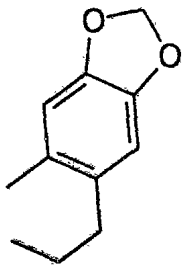
R^8 and R^9 are each $-CH_2-CH_2-Cl$, R^{10} is H and R^{11} + R^{12} together are $-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-$, as well as the salts thereof with pharmaceutically compatible acids.

2. Method according to claim 1, wherein as the phosphorous derivatives of alkaloids, the alkaloid derivatives of thiophosphoric acid of the general formula



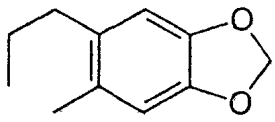
. (I)

wherein n is 1, 2 or 3; m is 1, 2 or 3; R^1, R^2 and R^3 independently each are hydrogen or methoxy, wherein R^1 and R^2 together or R^2 and R^3 together also may represent a methylenedioxy group; R^4 is hydrogen, hydroxy or methyl; and, if R^7 is hydrogen, R^5 and R^6 together form the group



;

or, if R^7 is a methyl group, the groups R^5 and R^6 represent the group



;

and in positions 1, 8 and/or 2, 3 a double bond may be present; and A is a monovalent or the equivalent portion of a polyvalent anion, are used.

3. Method according to claim 1 or 2, wherein the reaction product of the alkaloids of chelidonium majus L. with thiophosphoric acid triaziridide is used.

4. Method according to any one of claims 1 to 3, wherein the endocrinopathy is osteoporosis.

5. A method according to claim 1 substantially as hereinbefore described.

DATED: 26 November, 1997

PHILLIPS ORMONDE & FITZPATRICK
Attorneys for:
WASSYL NOWICKY

ABSTRACT:

The invention concerns the use of phosphorus derivatives of alkaloids of the general formula (I), as disclosed in AT PS 377 988 and AT PS 354 644, for preparing a medicament for treating endocrinopathies, in particular for treating osteoporosis.

INTERNATIONAL SEARCH REPORT

Interna l Application No
PCT/AT 95/00055

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/675

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US-A-4 816 462 (WASSYL NOWICKY) 28 March 1989 see the whole document ---	1-4
A	DRUGS UNDER EXPERIMENTAL AND CLINICAL RESEARCH, vol. 18, 1992 pages 93-96, KLEINROK, Z. ET AL 'SOME PHARMACOLOGICAL PROPERTIES OF PROLONGED ADMINISTRATION OF UKRAIN IN RODENTS' see the whole document --- -/--	1-4

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 June 1995	04. 07. 95
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	**Authorized officer** Mair, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/AT 95/00055

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DRUGS UNDER EXPERIMENTAL AND CLINICAL RESEARCH, vol. 18, 1992 pages 85-87, JAGIELLO-WOJTOWICZ, E. ET AL 'EFFECT OF SINGLE AND THREE MONTHS TREATMENT WITH UKRAIN ON AMINOTRANSFERASES (ALT AND AST) AND ON THE SERUM PROTEIN LEVEL IN RODENTS' see the whole document ---	1-4
A	DRUGS UNDER EXPERIMENTAL AND CLINICAL RESEARCH, vol. 18, 1992 pages 89-91, JAGIELLO-WOJTOWICZ, E. ET AL 'EFFECT OF PROLONGED ADMINISTRATION OF UKRAIN ON PROLACTIN CONCENTRATION IN RATS' see the whole document ---	1-4
A	EP-A-0 326 627 (VIPOINT PHARMACEUTICAL INC.) 9 August 1989 see the whole document -----	1-4

INTERNATIONAL SEARCH REPORT

Ir ational application No.
PCT/AT95/00055

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-4
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Wegen der grossen Zahl der Verbindungen, die die Formel in den Ansprüchen 1 und 2 theoretisch definiert, musste die Recherche aus ökonomischen Gründen eingeschränkt werden. Die Recherche beschränkte sich auf die bevorzugten Verbindungen und das allgemeine erfinderische Konzept.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat Application No
PCT/AT 95/00055

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-4816462	28-03-89	AU-B-	566682	29-10-87
		AU-A-	8597782	24-02-83
		PT-A-	75226	25-05-83
		US-A-	4970212	13-11-90
EP-A-326627	09-08-89	US-A-	4735945	05-04-88