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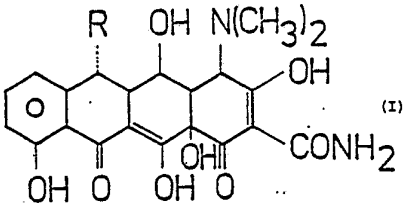
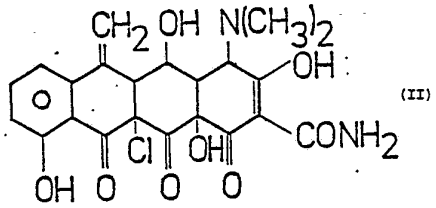


(I)



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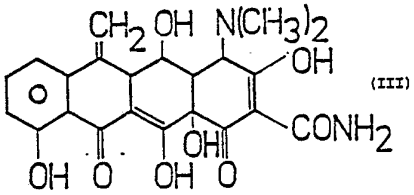

(III)

(57) Abstract

The invention relates to a process for the preparation of tetracycline derivatives of formula (I), and acid addition salts thereof, wherein R stands for $-CH_3$ or $=CH_2$, by dehalogenating and hy drating chloromethacycline or acid addition salt thereof of formula (II), or by hydrating methacycline or acid addition salts thereof of formula (III), by a treatment with hydrogen gas in the presence of a noble metal alloy catalyst on carrier and organic solvent which comprises performing hydrating under pressure of 0.1-1.0 MPa with an alloy catalyst consisting of the alloy palladium or platinum and selenium and/or tellurium used at a ratio of 1:0.01-0.5 related to the amount of the starting tetracycline and carrying out, if desired dehalogenation and hydration in one step.

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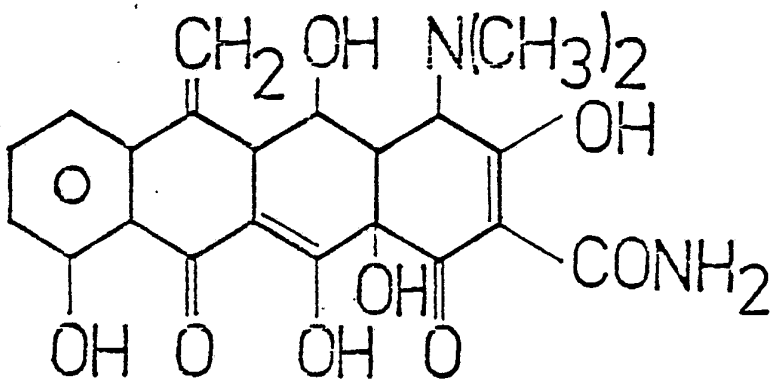
IMPROVED PROCESS FOR THE PREPARATION OF TETRACYCLINE DERIVATIVES

The present invention relates to an improved process for the preparation of doxycycline and methacycline and acid addition salts thereof by catalytic dehalogenation and hydrogenation by using a tellurian and/or selenium containing alloy catalyst latter being prepared according to this invention as well.

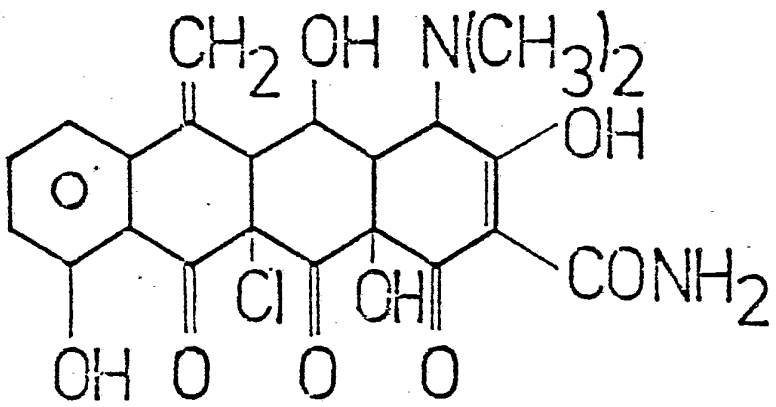
The following abbreviations are used throughout the specification:

"methacycline": 4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methylene-1,11-dioxo-2-naphtacene-carboxamide of the formula



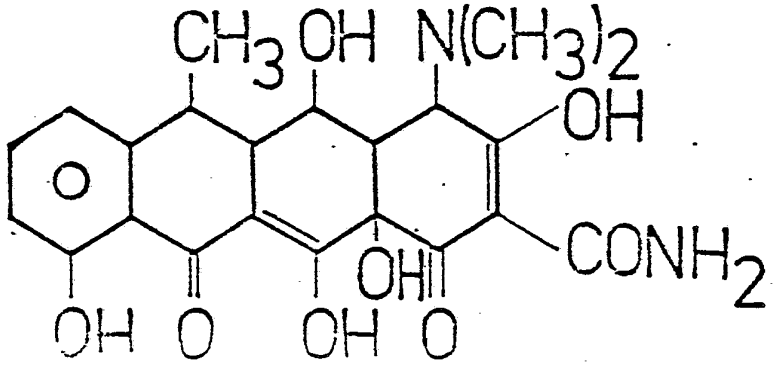
III.

"chloro-methacycline": 4-dimethylamino-1,4,4a,5,5a,6,11,12-12a-nonahydro-3,5,10,12a-tetrahydroxy-11a-chloro-6-methylene-1,11,12-trioxo-2-naphtacene-carboxamide of the formula



II.

"doxycycline": α -6-desoxy-5-hydroxy-tetracycline, i.e. 4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12-12a-pentahydroxy-6α -methyl-1,11-dioxo-2-naphtacene-carboxamide of the formula



IV.

"β-doxycycline" is the β-isomer of doxycycline

R stands for $-CH_3$ or $=CH_2$

It is known that methacycline and doxycycline are very effective representatives of the tetracycline type antibiotics.

Several processes are known for the preparation thereof using oxytetracycline as starting material and preparing chloromethacycline followed by dehalogenation and if desired by hydrating the obtained methacycline to doxycycline.

Dehalogenation was solved - among other methods - by introducing hydrogen gas in the presence of a catalyst, see e.g. Example 9 of HU-PS 150909, wherein rhodium precipitated on active coal was used.

This process, however, was not satisfactory as reaction products were produced which were difficult to separate from side-products and the conversion was not complete either. Therefor the use of secondary or tertiary phosphines has been recommended in HU-PS 169 605. This process was accompanied with the disadvantage that an equimolar amount of tertiary or secondary phosphines was needed, resulting in a great amount of waste, being poisonous, and the formed phosphine oxide could be converted again to phosphine only by a multi-step reaction.

The introduction of hydrogen gas in the presence of a catalyst was also used for the saturation of the double bond of the methylene group at the 6-position on methacycline in order to produce doxycycline.

In the course of hydration 6-desoxy-5-hydroxy-tetracycline of the formula (IV) can occur in the form of α- and β-isomers. Only the α-isomer is valuable as medicine, i.e. doxycycline. The amount of the α-isomers during hydration determines if the hydration process is successful, i.e. if hydrogenation can be carried out selectively, to produce mainly α-isomer with good yield and pure quality.

It has been known that 6-desoxy-5-hydroxy-tetracycline could be prepared with a yield of 60 % by using a 5 % palladium or rhodium catalyst on a carrier, but the product was a 1:1 mixture of α- and β-isomers, which was followed by the separation of the α-isomer accompanied by further losses (US-PS 3 200 149). The ratio of the formation of the α-isomer can considerably be improved, if the noble metal catalyst on a carrier is poisoned by carbon monoxide, quinoline sulphur or other sulphur compounds. Thus the yield of the α-isomer could be increased to 40-50 %, but even so the product had to be further purified due to the remaining 10 % β-isomer impurities (HU-PS 156 925). In order to improve the stereoselectivity of hydrogenation an alloy catalyst consisting of the metals of platinum group, copper, silver or gold has been used and a doxycycline yield of about 70 % has been disclosed with 1 to 10 % β-isomer impurities (HU-PS 167 250).

A 92 % α-isomer content has been achieved by using a catalyst containing palladium atoms located on ultra-microporous active coal, without poisoning, with a yield of 76 % (HU-PS 169 667).

Hydration could be performed by using Raney nickel and Raney cobalt as a catalyst according to GB-PS 1 296 340, but the formation of α-isomer in the reaction mixtures amounted only to about 40 %. According to Finnish PS 67210 to palladium/charcoal catalyst a complex of bis-

(diphenylselenide) palladium(II)chloride was added resulting thus in a yield of 75 %, wherein the ratio of the α-isomer was about 95 %. According to the disclosure this effect could not be achieved if diphenylselenide was not used in a complex form.

In order to give a complete review of the known processes, we mention those hydration processes, which are not close to our process, but wherein hydration was performed by using triphenyl phosphine rhodium complexes, being catalysts which are soluble in the reaction mixture (DE-OS 2 403 714) or by using further additives next to the complexes (HU-PS 169 753, 169 508, 173 508 and 187 465).

Doxycycline could thus be prepared with a good yield and selectivity.

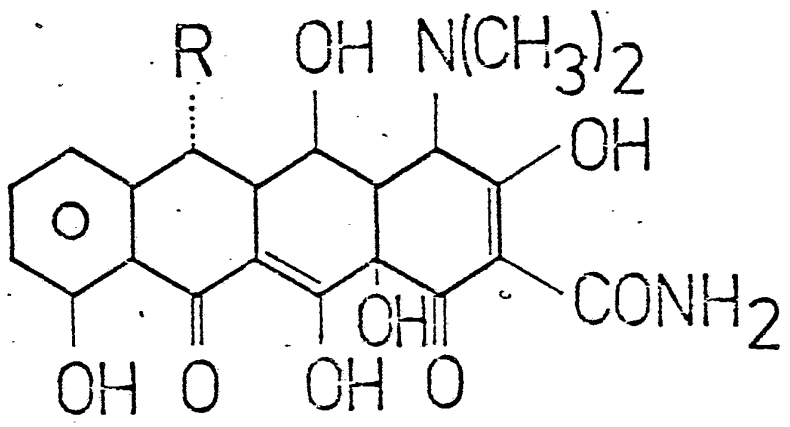
Inspite of the significant development the known processes show many drawbacks. As already mentioned the use of the known heterogeneous catalysts does only partially solve the problem of stereoselectivity. A considerable amount of these catalysts had to be used, and so the ratio substrate-catalyst was not favourable. The relative great amount of the used solvent was also unfavourable. Although the catalysts can be removed from the reaction mixture by filtration, the solvent has to be recovered before use by a costly and inefficient procedure.

In case of homogeneous catalysis the catalyst is

in solution, its isolation is not easy. Rhodium is very expensive, it is difficult to obtain, its recovery is complicated, expensive and it can contaminate the product.

According to the present invention methacycline and doxycycline resp. are prepared by process in heterogeneous layer, wherein dehalogenation can be performed with good yield and reduction takes place stereoselectively and the side reactions can be eliminated to such extent that no extra purification of the product is needed and the used catalyst can be prepared simply and the specific costs of the catalyst are low. It was further aimed that dehalogenation and hydration can be prepared without any extra equipment by using the same type of catalyst. Thus the just needed medicine can be prepared.

The present invention is directed to a process for the preparation of tetracycline derivatives and acid addition salts thereof of the general formula (I) .



I.

by dehalogenating and hydrating chloromethacycline or acid addition salt thereof of the formula II or by hydrating methacycline or acid addition salt thereof of the formula III by a treatment of same with hydrogen gas in the presence of a noble metal alloy catalyst on a carrier in the presence of an organic solvent comprising carrying out the hydrogenation at a pressure of 0.1-1.0 MPa with an alloy catalyst used at a ratio of 1:0.01-0.5 related to the starting tetracycline derivative consisting of an alloy of palladium or platinum or selenium and/or tellurium and performing, if desired the dehalogenation and hydration in one step.

As a carrier e.g. active charcoal, silica or aluminium oxide can be used.

In order to prepare the noble metal-containing catalyst one may proceed by treating the aqueous suspension of palladium or platinum on a carrier with a solution or suspension of organic or inorganic selenium or tellurium compounds and optionally by reducing the obtained compound. Such compounds can be selected from salts, oxides and other derivatives, such as selenious acid, diphenyl selenide etc.

One may use a different method according to which palladium or platinum salts and selenium or tellurium compounds may be dissolved in acidic water and a carrier, preferably active charcoal can be added to the carrier, followed by reduction.

The noble metal content of the catalyst may vary between 1 to 30 % by weight, preferably 5 to 10 % by weight, the used noble metal can be selected from palladium and platinum and the amount of the alloying components may vary between 1 to 70 % by weight related to the amount of the noble metal content.

As a solvent preferably lower alcohols, ketones, N,N-dialkyl amides, water and mixtures thereof may be used. It is not necessary to dissolve the starting material completely.

According to a preferred method methacycline may be prepared by saturating chloromethacycline with equimolar hydrogen gas at a pressure of 0.1-0.3 MPa in the presence of an alloy catalyst selected from palladium-selenium, palladium-tellurium, platinium-selenium and platinium-tellurium by using the catalyst in an amount of 1:0.01-0.2 related to the weight of chloromethacycline, wherein the amount of the alloying components amounts to 20-70 % by weight related to the noble metal content.

Methacycline may be recovered from the reaction mixture by any known method in the form of a base, acid addition salt or complex.

Main advantages of the dehalogenation according to the present invention: dehalogenation can be performed

without side reactions, the conversion of methacyclines to 5-12a lactones can be suppressed, the reaction takes place at atmospheric pressure and room temperature within a short time, the catalyst can be prepared simply and it is not pyrophoric or its activity does not weaken under storing or in the course of the reaction, thus it can be used several times without regeneration, thus the catalyst costs of the process are minimal, almost negligible.

In order to obtain doxycycline metacycline or chlorometacycline or a salt thereof can be treated with hydrogen gas in the presence of an alloy catalyst consisting of palladium-selenium, palladium-tellurium, platinum-selenium or platinum-tellurium at a pressure of 0.1-1.0 MPa with an amount of catalyst of 1:0.05-0.5, preferably 0.15-0.25 related to the weight of methacycline, the amount of the alloying components is 1 to 40 % by weight.

If chloromethacycline or salts thereof are used as starting material then dehalogenation and the selective saturation of the double bond can be performed in one single step. As a solvent lower alcohol, ketones, dimethyl-formamide, water and mixtures thereof are used.

When the reaction is terminated the catalyst is filtered and may be used for further reactions. The product may be isolated from the filtrate by any known method, such as in the form of a salt of hydrogen halogenic acid, 5-

sulfo salicylic acid or in the form of hyclates.

Main advantages of the process for the preparation of doxycycline are as follows:

- the saturation of the exocyclic methylene bond in methacycline takes place substantially stereoselectively, i.e. the β-isomer content is reduced in doxycycline below 1 % by weight (according to HPLC),
- in the reactions starting with chloromethacycline dehalogenation and hydration can be carried out in one single technological step, the reaction can be performed at atmospheric pressure and room temperature within a short time,
- the catalyst can be rapidly prepared simply, it is not pyrophoric, and its activity does not decrease under storing or in the course of the hydration reaction and thus the catalyst costs of the process are minimal, almost negligible,
- the process may be continualized,
- the isomerisation side reaction occurring in heterogeneous catalytical reactions, causing intensive decomposition are suppressed and therefor doxycycline can be obtained with good yield. This experience is highly suprising as the selenium is known to act as a catalyst in oxidation and isomerisation reactions.

Further details of the invention can be found in the following Examples:

Example 1

10 g 10 % by weight palladium/charcoal catalyst are suspended in 100 ml of water and 0.1 to 0.7 g of selenious acid are added as desired and the mixture is subjected to hydrogenation at room temperature under stirring. The mixture is then filtered, washed with water and acetone and dried. The activity of the catalyst is measured.

Example 2

1.33 g of palladium(II)chloride and 0.2-0.7 g of tellurium(IV)oxide are dissolved in 100 ml of 6N hydrochloric acid, whereafter 10 g of charcoal are added and the mixture is stirred for 3 hours and hydrated with hydrogen gas. The catalyst is filtered, washed to neutral and dried. Its activity is measured.

Example 3

5 g of 10 % by weight palladium/charcoal catalyst are suspended in 50 ml of ethanol, and as desired 0,15-1 g of diphenyl selenide are added, the suspension is boiled for 30 minutes, the catalyst is filtered and dried. Its activity is measured.

Example 4

10 g of 5 % by weight palladium/silica catalyst are suspended in 100 ml of water and as desired 0.1-0.4 g of selenious acid are added and we further proceed as given

in Example 1. The activity is measured.

Example 5

10 g of 5 % by weight platinum/active charcoal catalyst are suspended in 100 ml of water and as desired 0.05 g to 0.4 g of selenious acid are added and we further proceed as disclosed in Example 1.

Example 6

1.77 g of palladium(II)chloride and as desired 0.1-0.75 g of selenium dioxide are dissolved in 80 ml of 12 N hydrochloric acid and 5 g of silicagel are added, the mixture is hydrated, filtered and dried. Its activity is measured.

The activity of the catalysts prepared according to the above Examples are qualified by a method known per se, by hydrating a cyclohexene model compound.

Preparation of methacycline

Examples 7 to 12

20 g of 11a-chloro-methacycline-p-toluene-sulfonate are reacted with hydrogen gas in 200 ml of solvent by using 1-3 g alloy on carrier catalyst at room temperature at a pressure of 0.1-0.3 MPa. When the equimolar amount of hydrogen is taken up, the catalyst is filtered off, and working up may be performed as desired as follows:

a) 20 g of 5-sulfosalicylic acid are added, it is crystallized and methacycline sulfosalicylate is isolated, or
b) the filtrate is evaporated in vacuo, and 75 ml of methanol and 7.5 g of p-toluene sulfonic acid are added to the residue. The mixture is crystallized and methacycline tosylate is isolated, or
c) the filtrate is evaporated in vacuo and 50 ml concentrated hydrochloric acid are added and methacycline hydrochloride is isolated. Yield: 85-95 %.

The quality of the products is thin layer chromatographically homogeneous (developing agent: a 95:5 mixture of tetrahydrofuran and water) on a silicagel carrier plate impregnated with a buffer of pH=6. Active ingredient content by biological value testing: 100 %.
The details are shown in Table I.

Table I

Example No.	Catalyst[+] pressure	Solvent[++]	Working up method	Product	Yield
7	1 g 5 % Pd/charcoal Se 20 %, 0.1 MPa	methanol-water 3:1	a)	20 g methacycline-sulfosalicylate	95.6 %
8	1 g 5 % Pt/charcoal Se 25 %, 0.2 MPa	acetone-water 4:1	a)	18.8 g methacycline-sulfosalicylate	90.0 %
9	2 g 10 % Pd/charcoal Se 40 %, 0.3 MPa	methyl-ethyl-ketone/water 4:1	b)	17.9 g methacycline tosylate	95.6 %
10	2 g 3.5 % Pd/charcoal Te 50 %, 0.3 MPa	methyl-ethyl-ketone/water 4:1	b)	16.4 g methacycline tosylate	88.0 %
11	2 g 5 % Pd/silicagel Se 30 %, 0.3 MPa	acetone-water 4:1	c)	12.45 g methacycline hydrochloride	87.0 %
12	1.5 g 10 % Pd/charcoal Se 30 %, 0.2 MPa	acetone-water 4:1	c)	12.2 g methacycline hydrochloride	85.0 %

[+] The noble metal content of the catalyst related to the weight of catalyst is given in % by weight and the amount of the alloying metal is determined in % by weight related to the noble metal content.

[++] The composition of the solvent is given in % by volume.

Preparation of doxycycline

Examples 13 to 20

47.3 g of methacycline hydrochloride or 63.6 g of methacycline p-toluene sulfonate are hydrated in 500-580 ml of solvent by using 3.5 to 10 g of an alloy catalyst on carrier at room temperature and a pressure of 0.1 to 1.0 MPa until the hydrogen uptake is completed. After filtering off the catalyst the filtrate can be worked up as follows:

a) 50 g of 5-sulfosalicylic acid are added to the filtrate and the product is crystallized and filtered, dried. Doxycycline sulfosalicylate is obtained as a product, or

b) the filtrate is evaporated in vacuo, 250 ml methanol and 25 g of p-toluene sulfonic acid are added to the residue, the mixture is crystallized and doxycycline tosylate is isolated, or

c) the filtrate is evaporated in vacuo, 180 ml of ethanol and 30 ml of hydrochloric acid are added to the residue and after dissolving and clarification 50 ml of hydrochloric acid and ethanol in hydrochloric acid are added to the filtrate. The mixture is crystallized and doxycycline hyclate is isolated, or

d) the filtrate is evaporated to dryness in vacuo, 250 ml of acetone are added to the residue and by introducing hydrochloric acid gas the doxycycline hydrochloride is recovered. Yield: 80-90 %. Quality of the product is homogeneous according to thin layer chromatography.

Active ingredient content by biological value testing: 100 %.

Ratio of α-isomer: 99 %, ratio of β-isomer: 0-0.6 %.

The details are shown in Table II.

Table II

Example No.	Catalyst[+] pressure	Solvent[++]	Working up method	Product	Yield
13	10 g 5 % Pd/charcoal Se 5 %, 0.3 MPa	acetone water 4:1	a)	62 g doxycycline-sulfosalicylate	89 %
14	5 g 5 % Pt/charcoal Se 8 %, 0.3 MPa	methyl-ethyl-ketone/water 4:1	a)	61.5 g doxycycline-sulfosalicylate	88 %
15	8 g 10 % Pd/charcoal Se 20 %, 0.4 MPa	acetone-water 4:1	b)	54.1 g doxycycline-tosylate	88 %
16	5 g 3.5 % Pd/charcoal Te 15 %, 0.5 MPa	methyl-ethyl-ketone/water 4:1	b)	50.5 g doxycycline-tosylate	82 %
17	10 g 5 % Pd/silicagel Se 10 %, 0.3 MPa	methyl-ethyl-ketone/water 4:1	c)	43.1 g doxycycline-hyclate	85 %
18	4 g 10 % Pd/charcoal Se 15 %, 0.3 MPa	acetone-water 4:1	c)	42.6 g doxycycline-hyclate	83 %
19	6 g 10 % Pd/charcoal Se 12 %, 0.2 MPa	acetone-water 4:1	d)	40.6 g doxycycline-hydrochloride	88 %
20	10 g 5 % Pd/silicagel Se 7 %, 0.3 MPa	methyl-ethyl-ketone/water 4:1	d)	39.2 g doxycycline-hydrochloride	85 %

[+] The nobel metal content of the catalyst related to the weight of catalyst is given in % by weight and the amount of the alloying metal is determined in % by weight related to the noble metal content.

[++] The composition of the solvent is given in % by volume.

Examples 21-28

66.7 g of 11a-chloro-methacycline-p-toluene-sulfonate are subjected to hydration in 500-580 ml of solvent by using 3.5 to 10 g of an alloy catalyst on carrier at room temperature and a pressure of 0.1 to 1.0 MPa until the hydrogen uptake is completed. After filtering off the catalyst the filtrate can be worked up as follows:

a) 50 g of 5-sulfosalicylic acid are added to the filtrate and the product is crystallized and filtered, dried. Doxycycline sulfosalicylate is obtained as a product, or

b) the filtrate is evaporated in vacuo, 250 ml methanol and 25 g of p-toluene sulfonic acid are added to the residue, the mixture is crystallized and doxycycline tosylate is isolated, or

c) the filtrate is evaporated in vacuo, 180 ml of ethanol and 30 ml of hydrochloric acid are added to the residue and after dissolving and clarification 50 ml of hydrochloric acid and ethanol in hydrochloric acid are added to the filtrate. The mixture is crystallized and doxycycline hyclate is isolated, or

d) the filtrate is evaporated to dryness in vacuo, 250 ml of acetone are added to the residue and by introducing hydrochloric acid gas the doxycycline hydrochloride is recovered. Yield: 80 -90 %. Quality of the product is homogeneous according to thin layer chromatography.

Active ingredient content by biological value testing: 100 %.
Ratio of α-isomer: 99 %, ratio of β-isomer: 0-0.6 %.
The details are shown in Table III.

Table III

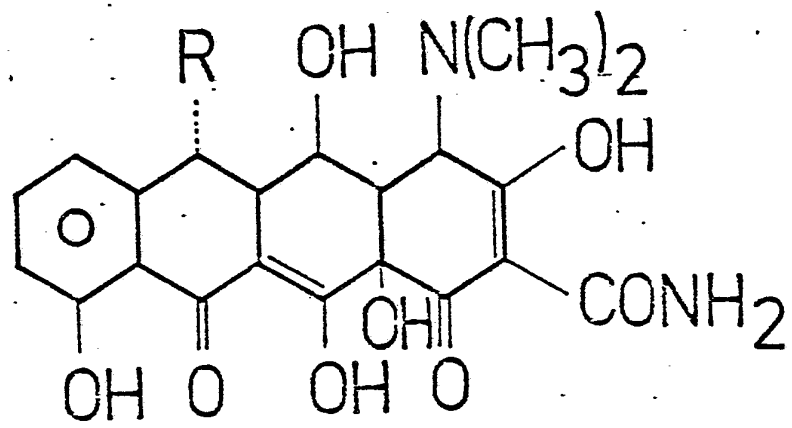
Example No.	Catalyst[+]	Solvent[++]	Pressure MPa	Working up method	Product	Yield
21	10 g 5 % Pd/charcoal Se 5 %	acetone-water 4:1	0.2-0.4	a/	61.5 g doxycycline sulfosalicylate	88 %
22	5 g 5 % Pd/charcoal Se 8 %	methyl-ethyl-ketone/water 4:1	0.2-0.4	a/	59.2 g doxycycline sulfosalicylate	88 % 85 %
23	8 g 10 % Pd/charcoal Se 20 %	acetone-water 4:1	0.3-0.5	b/	53.6 g doxycycline-tosylate	87 %
24	5 g 3.5 % Pd/charcoal Te 15 %	methyl-ethyl-ketone/water 4:1	0.4-0.5	b/	50.5 g doxycycline-tosylate	82 %
25	10 g 5 % Pd/silicagel Se 10 %	methyl-ethyl-ketone/water 4:1	0.2-0.4	c/	42.1 g doxycycline-hyclate	82 %
26	4 g 10 % Pd/charcoal Se 15 %	acetone-water 4:1	0.4-0.5	c/	42.1 g doxycycline-hyclate	82 %
27	6 g 10 % Pd/charcoal Se 12 %	acetone-water 4:1	0.2-0.3	d/	39.2 g doxycycline-hydrochloride	85 %
28	10 g 5 % Pd/silicagel Se 7 %	methyl-ethyl-ketone/water 4:1	0.2-0.3	d/	38.3 g doxycycline-hydrochloride	83 %

[+] The nobel metal content of the catalyst related to the weight of catalyst is given in % by weight and the amount of the alloying metal is determined in % by weight related to the nobel metal content.

[++] The composition of the solvent is given in % by volume.

CLAIMS:

1. Process for the preparation of tetracycline derivatives of the formula

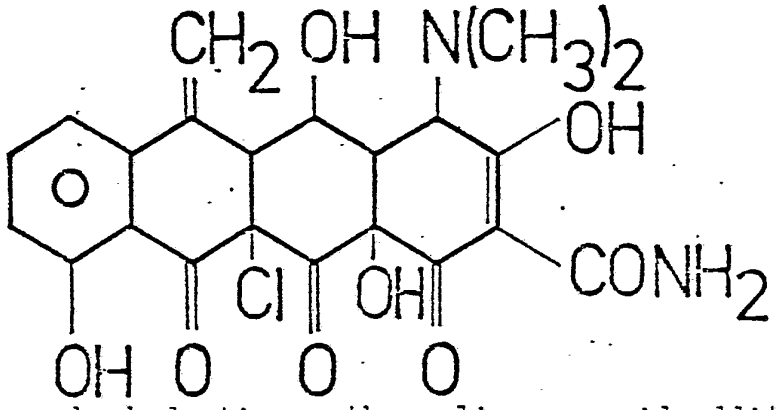


I.

and acid addition salts thereof

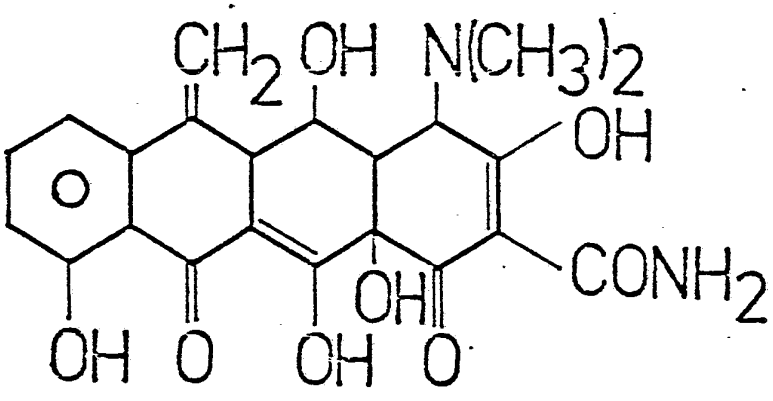
wherein R stands for $-CH_3$ or $=CH_2$

by dehalogenating and hydrating chloromethacycline or acid addition salt thereof of the formula



II.

or by hydrating methacycline or acid addition salts thereof of the formula



III.

by a treatment with hydrogen gas in the presence of a noble metal alloy catalyst on carrier and organic solvent which comprises performing hydrating under pressure of 0.1-1.0 MPa with an alloy catalyst consisting of the alloy palladium or platinum and selenium and/or tellerium used at a ratio of 1:0.01-0.5 related to the amount of the starting tetracycline and carrying out, if desired dehalogenation and hydration in one step.

2. Process as claimed in claim 1 which comprises preparing methacycline by saturating chloromethacycline with equimolar hydrogen gas in the presence of an alloy catalyst on carrier of palladium-selenium, palladium-tellurium or platinum-selenium or platinum-tellurium under a pressure of 0.1-0.3 MPa at a ratio of 1:0.01-0.2 catalyst related to the amount of chloromethacycline, wherein the amount of selenium and/or tellurium amounts to 20-70 % by weight related to the amount of palladium and/or platinum.

3. Process as claimed in claim 1 which comprises preparing doxycycline by treating methacycline or salts thereof with hydrogen gas in the presence of alloy on carrier catalyst consisting of palladium-selenium, palladium-tellurium, platinum-selenium or platinum-tellurium at a pressure of 0.1-1 MPa at a ratio of 1:0.05-5 catalyst related to the weight of methacycline, wherein the amount of the alloying components amounts to 1-40 % by weight.

4. Process as claimed in claim 1 which comprises preparing doxycycline by treating chloromethacycline or salts thereof with hydrogen gas in the presence of alloy on carrier catalyst consisting of palladium-selenium, palladium-tellurium, platinum-selenium or platinum-tellurium at a pressure of 0.1-1 MPa at a ratio of 1:0.05-5 catalyst related to the weight of methacycline, wherein the amount of the alloying components amounts to 1-40 % by weight.

5. Process as claimed in any of the claims 2 to 4 which comprises using water, alcohols, ketones, preferably methanol, propanol, dimethylformamide, acetone, methyl ethyl ketone or mixtures thereof as a solvent.

6. Process as claimed in any of the claims 1 to 4 which comprises using as alloys for hydration alloys which contain 1-70 % by weight of selenium or tellurium and 99-30 % by weight of palladium or platinum.

7. Process for preparing an alloy-catalyst as claimed in claim 1 which comprises treating an aqueous suspension of palladium- or platinum catalyst on a carrier with a solution or suspension of organic or inorganic selenium or tellurium compounds and optionally reducing the obtained compounds.

8. Process for preparing an alloy catalyst as claimed in claim 1 which comprises dissolving palladium or platinum salt and selenium or tellurium compound in acidic water, adding a carrier, preferably active charcoal to the mixture and reducing the obtained compound.

INTERNATIONAL SEARCH REPORT

International Application No PCT/HU 88/00063

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: C 07 C 103/19; B 01 J 27/057

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
Int.Cl.[4]	C 07 C 103/19; B 01 J 27/057,23/54,23/56,27/00, 27/02,35/00,35/02,37/16,37/18

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

AT

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	FI, B, 67 210 (SUOMEN LÄÄKETEHDAS OY SALCO) 31 October 1984 (31.10.84).	(1-8)
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* Special categories of cited documents: [10]

"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

"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

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
11 November 1988 (11.11.88)	22 November 1988 (22.11.88)
International Searching Authority	**Signature of Authorized Officer**
AUSTRIAN PATENT OFFICE	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

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A	Chemical Abstracts, Volume 89, no. 14, issued 1978, October 2 (Columbus, Ohio, USA), S. Bhan et al. "Ordered bcc. phases at high temperatures in alloys of transition metals and A-subgroup elements" see page 786, the abstract no. 121 060r, Z. Metallkd. 1978, 69(5),333-6(Eng.).	(7,8)
A	Chemical Abstracts, Volume 102, no. 4, issued 1985, January 28 (Columbus, Ohio, USA), S. G. Rybkin et al. "Platinum,-tellurium system" see page 570, the abstract no. 33 485q, Izv. Akad. Nauk SSSR, Neorg. Mater. 1984, 20(5), 828-30(Russ).	(7,8)
P,A	Chemical Abstracts, Volume 107, no. 18, issued 1987, November 2, (Columbus, Ohio, USA), T. Takabatake et al. "Superconductivity and phase relations in the palladium-selenium system" see page 559, the abstract no. 162 723f, J. Less-Common Med. 1987, 134(1), 79-89(Eng.).	(7,8)

Anhang zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

Annex to the International Search Report on International Patent Application No. PCT/HU 88/00063

Annexe au rapport de recherche internationale relatif à la demande de brevet international n°.

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned International search report. The Austrian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche internationale visé ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsabilité de l'Office autrichien des brevets.

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