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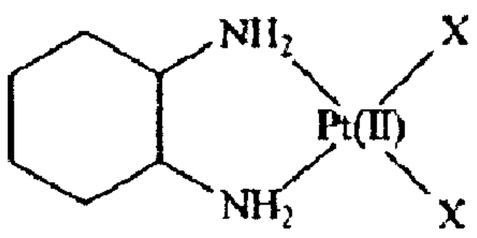
(54) Titre : SYNTHESE DE COMPLEXES DE 1,2-DIAMINOCYCLOHEXANE-PLATINE (II)
(54) Title: PROCESS FOR THE PREPARATION OF 1,2-DIAMINOCYCLOHEXANE-PLATINUM(II) COMPLEXES

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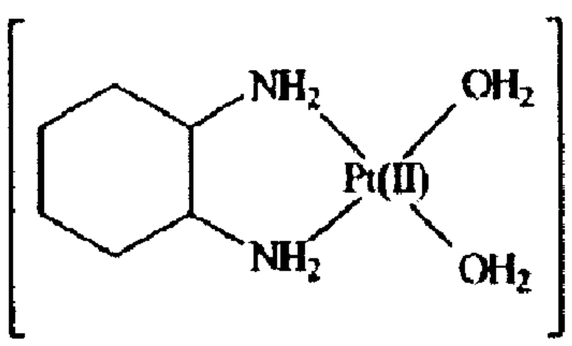


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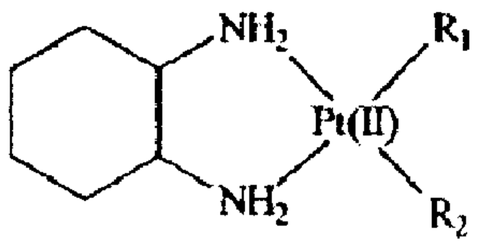


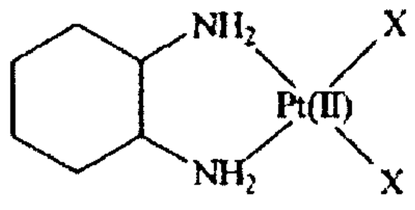

(1)

(57) Abrégé/Abstract:
A process for the preparation of diaminocyclohexane-platinum(II)-dicarboxylates has the following steps: B Conversion of $K_2PtX_2$ with 1,2-diaminocyclohexane (DACH) to (see formula 2) C Conversion of (2) with too little quantity of silver salt $Ag_nA$ to (see formula 3) and removal of the resulting AgX precipitate. (see formula 1) D Conversion of (3) with a dicarboxylate to F Isolation of the product (1), whereby $R_1$ and $R_2$ together form a dicarboxylato group, X stands for Cl or I, A for a 1-2-valent anion of a mineral acid and n stands for 1 or 2.

## Abstract

A process for the preparation of diaminocyclohexane-platinum(II)-dicarboxylates has the following steps:

B Conversion of $K_2PtX_2$ with 1,2-diaminocyclohexane (DACH) to

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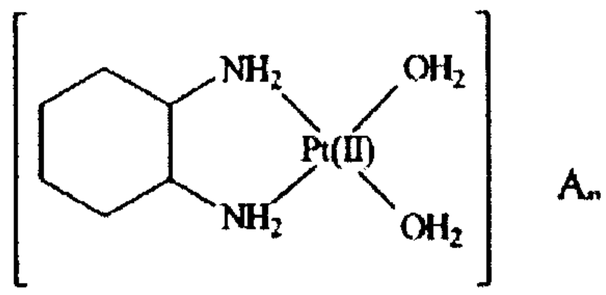
C Conversion of (2) with too little quantity of silver salt $Ag_nA$ to

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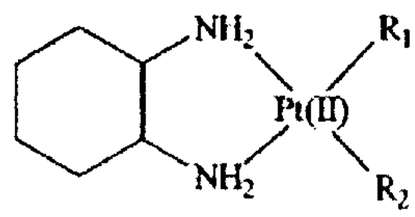
and removal of the resulting AgX precipitate.




(1)

D Conversion of (3) with a dicarboxylate to

F Isolation of the product (1),

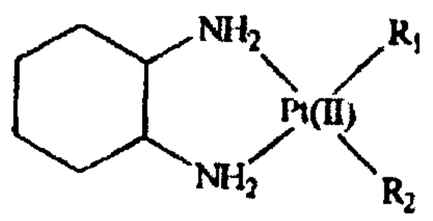
whereby $R_1$ and $R_2$ together form a dicarboxylato group, X stands for Cl or I, A for a 1-2-valent anion of a mineral acid and n stands for 1 or 2.

**Process for the preparation of 1,2-diaminocyclohexane-platinum(II) complexes**

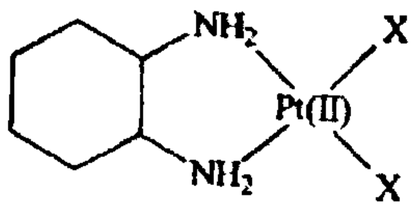
The invention concerns a process for the preparation of 1,2-diaminocyclohexane-platinum(II) complexes, particularly diaminocyclohexane-platinum(II)-dicarboxylate complexes such as oxaliplatinum.

*Cis* platinum(II) complexes with 1,2-diaminocyclohexane ligands are used for instance as active ingredients for the production of antitumoractive preparations (B. Lippert, ed. Cisplatin, Wiley VCH 1999).

Examples of platinum complexes with antitumor activity are compounds of the formulas (1), (2), (3):




**(1)**

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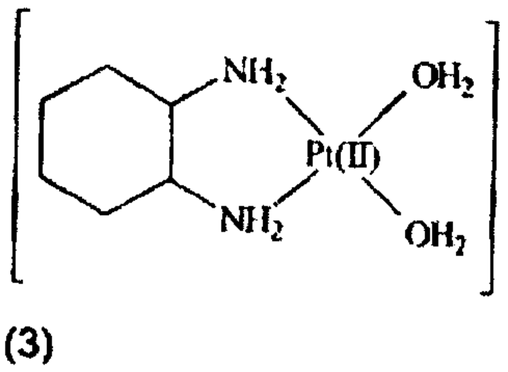
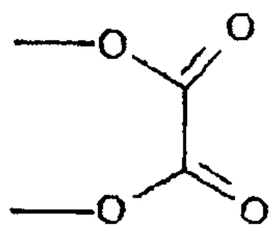



**(3)**

whereby $R_1$ and $R_2$ together form a dicarboxylato group, X stands for Cl or I, A stands for a univalent or bivalent anion and n stands for 1 or 2.

The present description of the process for the preparation of *cis*-platinum compounds refers preferentially to oxaliplatinum [$R_1$ and $R_2$ form together a moiety of the formula (4)]



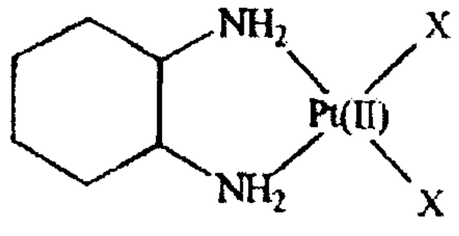
(4)

The task is to make prepare diaminocyclohexane-platinum(II)-dicarboxylate complexes of a quality that meets one or more of the following requirements:

1. high purity, particularly lower Ag content;
2. meets or exceeds requirements of the EP (European Pharmacopoeia, 4th edition, 2002, supplement 4.4);
3. no recrystallization is necessary for the purification of the end product;
4. can be obtained in high yield;
5. particular suitability of the active ingredient for parenteral applications.

The task is solved by a process for the preparation of diaminocyclohexane-platinum(II) dicarboxylates with the following steps:

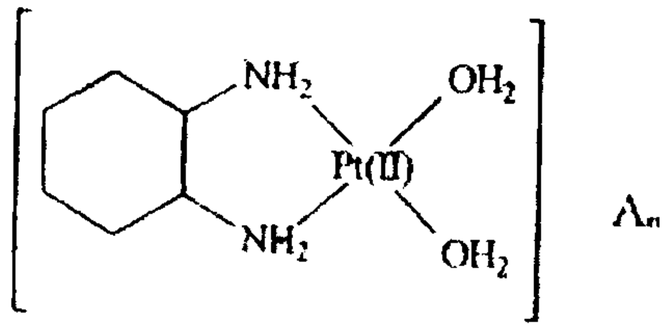
B Conversion of $K_2PtX_4$ with 1,2-diaminocyclohexane (DACH) to




(2)

C Conversion of (2) with a silver salt $Ag_nA$ to

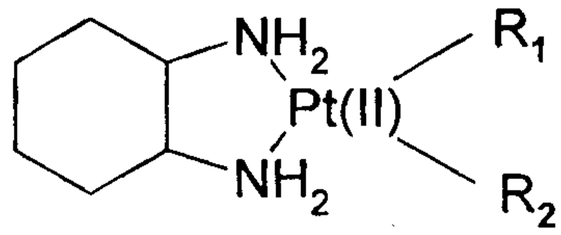
(2)




(3)

and removal of the resulting AgX precipitate.

D Conversion of (3) with a dicarboxylate to (1)



(1)

with $R_1$, $R_2$ = dicarboxylate

F Isolation of the product from D; and also if necessary

G Washing of the obtained product with water and methanol (or another low boiling solvent that is pharmacologically acceptable),

whereby in step C a silver salt is used. Thus during the synthesis, the compound of formula (2) is converted using less than a stoichiometric amount of silver salt, i.e. less than 2 mole equivalents of silver salt, in order to ensure a lower silver content in the product.

The optical and isomeric purity of the product of the process depends first on the quality of the chiral ligands 1,2-diaminocyclohexane. It is preferable to use 1,2-diaminocyclohexane of high optical and isomeric purity. Usually products of the required purity are available commercially. If not, commonly used purification processes are available such as cocrystallization and distillation.

A: $K_2PtCl_4 + 4KI \rightarrow K_2PtI_4 + 4\ KCl$

During the synthesis it is convenient to start from $K_2PtCl_4$ (optional step A). It is, of course, also possible to start directly from $K_2PtI_4$ (starting from step B). Furthermore, it is also possible to directly convert $K_2PtCl_4$ with DACH. However due to the low solubility of the Ag precipitate, the iodide enhances the prospects for the purity of the end product.

The following characteristics of the procedure have proved to be advantageous. They can be used individually or in combination with each other in the procedure in accordance with the present invention:

C The reaction mixture from the silver reaction is cooled before the filtration to less than 10 degrees C. Thus the precipitate is removed as thoroughly as possible and the product contains little silver.

D The dicarboxylate and/or oxalate is used in the form of its ammonium salt – either as free compound or prepared in situ from dicarbon acid and/or oxalic acid and ammonia.

E Before step F a single or a more beneficial a twofold treatment with activated carbon is carried out conveniently. This leads to a very low content of contaminants particularly with the intermediate product 1,2-diaminocyclohexane-diiodo-platinum(II). After the analysis the end product usually contains less than 0.02 % 1,2-diaminocyclohexane-diiodo-platinum.

A-F For all reaction steps purified endotoxin-free water with a limited bacteria content ("purified water" in accordance with EP 4 and/or USP 27) is used. The highly purified water in accordance with EP 4 (European Pharmacopoeia, 4$^{th}$ edition, 2002) is particularly suitable.

F Before the crystallization of the product the solution is filtered via a sterile filter. Thus the resulting product is very well-suited for the preparation of infusion solutions.

G After the last washing process with water, the platinum compound is washed additionally with methanol (or with another low boiling solvent that is pharmacologically acceptable). This leads to very short drying time and less water content (and a small content of aqua species, compound (3)) in the product.

If several or all process steps are combined, the compound produced in accordance with this procedure does not have to be purified by recrystallization in order to meet the specifications required by the European Pharmacopoeia (4$^{th}$ edition).

The compound prepared in accordance with the present invention has no melting point in the range of 198 to 292 degrees C (as stated in US 5,338,874) also no melting point in the range of 198.3 to 199.7 degrees C (according to US 5,420,319) and instead shows a decomposition range from 272 to 303 degrees C more specifically a decomposition range of 286 to 299 degrees C. Yet the crystal structure of the derived platinum compound is identical to the published structure (Lit. Ref.: Bruck, M.A.; et al., Inorg. Chim. Acta, 92 (1984)).

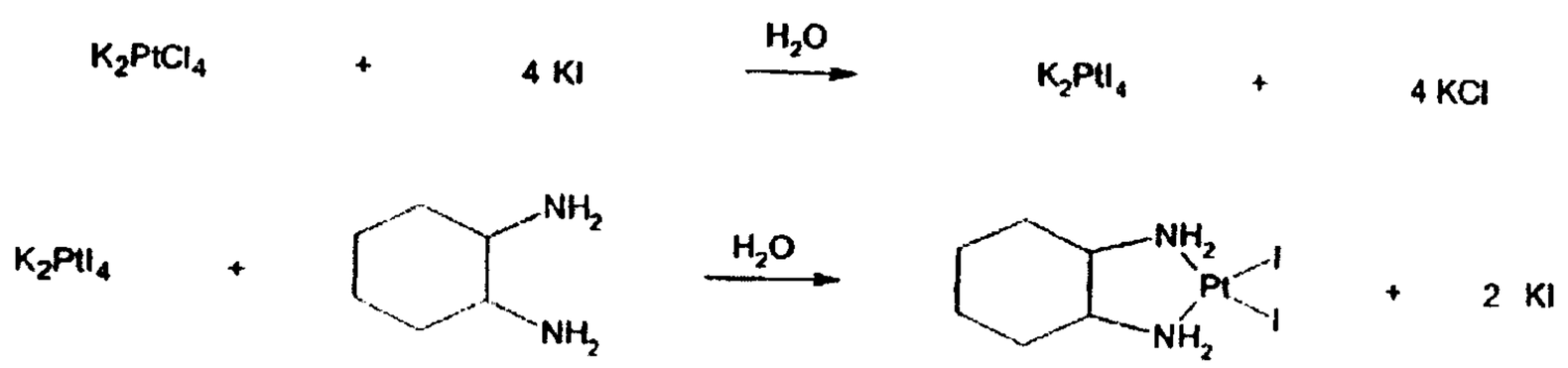
The present invention particularly describes a procedure for the preparation of oxaliplatinum [oxalato-(trans-1-1,2-cyclohexandiamine)platinum(II); CA Reg. No. 61825-94-3] in accordance with formula (1) with the following reaction steps (diagram 1 and diagram 2):

Preliminary product: Isomer/enantiomer-pure diaminocyclohexane, purified by crystallization with suitable tartrate salts and/or distillation.

First synthesis step: Preparation of 1,2-diaminocyclohexane-diiodo-platinum(II)

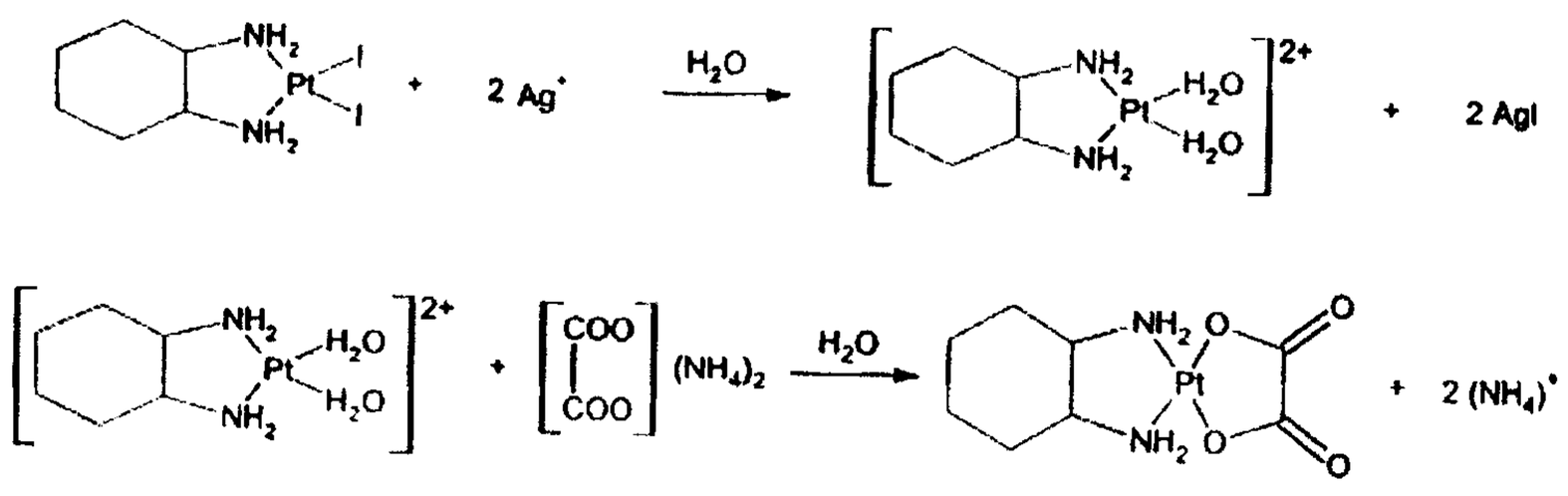
Reaction of potassium tetrachloroplatinate ($K_2[PtCl_4]$) with potassium iodide (KI) and 1,2-diaminocyclohexane, whereby first diiodo-compounds are derived in accordance with the formula (2), X=I.

Diagram 1:




The derived intermediate compound can be introduced after being filtered and washed with water either directly or after being dried in the next reaction step (diagram 2).

Diagram 2: Second synthesis step: Preparation of oxaliplatinum




- The reaction with soluble silver salt (e.g. silver nitrate, silver sulfate, and such) takes place by resuspending the 1,2-diaminoxycylcohexane-diiodo-platinum(II) (filter cake or dried material) and by adding (based on the platinum quantity used in potassium tetrachloroplatinate) a hypostoichiometric amount, (less than 2 mole equivalents) of soluble silver salt. The hypostoichiometric amount of the soluble silver salt can lie in the range of 1.4 to 1.98 mole equivalents. A preferential amount of soluble silver salt lies in the range of 1.70 to 1.90 mole equivalents. A silver salt quantity in the range of 1.78 to 1.82 mole equivalents is particularly advantageous. The reaction with the silver salt is carried

out at temperatures of 20 to 70 degrees C within 2 to 24 hours. Subsequently the reaction mixture is cooled, preferably for 4 to 30 hours at temperatures of 4 to 10 degrees C and the resulting silver iodide is removed by filtration.

- The thus derived solution of the diaqua compound in accordance with formula (3) [counterion in the illustrated case is nitrate; it can also be sulfate or a similar ion is mixed with a solution of an excess of ammonium oxalate based on the used silver salt. The amount of ammonium oxalate generally lies in the range of 0.51 to 0.70 molar equivalents. 0.525 to 0.60 molar equivalents are preferred while 0.54 to 0.56 molar equivalents are particularly advantageous. The reaction with ammonium oxalate is carried out preferentially at temperatures of 20 to 70 degrees C within 2 to 24 hours.
- The thus obtained solution is mixed with an amount of 5 to 10 weight percentage of activated carbon, based on the potassium tetrachloroplatinate and agitated for 12 to 72 hours. The activated carbon is removed by filtration. A repetition of the described purification with activated carbon is very advantageous.
- The obtained solution is once again filtered via a sterile filter and concentrated to a suitable volume of e.g. less than 10 ml per gram of product.
- The obtained solution is filtered, washed and dried. It is beneficial to wash it 1-3 times with water ("purified water" in accordance with EP 4 and/or USP 27 or preferentially "highly purified water" in accordance with EP4, endotoxin-free) and 1-3 times with methanol (or another low boiling solvent that is pharmacologically acceptable) and dried at least 24 hours in a sterile air stream (at temperatures between 20 and 50 degrees C and pressure between 1 bar and $10^{-3}$ bars absolute).

The following example serves for the explanation of the invention without restricting it:

**Example 1**

$K_2[PtCl_4]$ (59.60g) is dissolved in water (439 ml). Potassium iodide (168.0 g) is dissolved in water (147 ml). Both solutions are combined and stirred for 30 min.

*Trans*-l-1,2-diaminocyclohexane (18.39 g) is dissolved in water (72 ml.) The solution is added to the platinum-containing solution while stirring and the agitation is continued for 72 hours. The obtained suspension is filtered. The filtered deposit is washed with water six times (200 ml) and subsequently dried. Yield of 1,2-diamonocyclohexane-diiodoplatinum II: 77.9 g (96%).

The obtained *Trans*-1-1,2 diaminocyclohexane-diiodo-platinum(II) is suspended in water (1389 ml) and the suspension is heated at 45 degrees C. Silver nitrate (43.91 g) is dissolved in water (139 ml) and this solution is combined with platinum-containing solution. The resulting mixture is

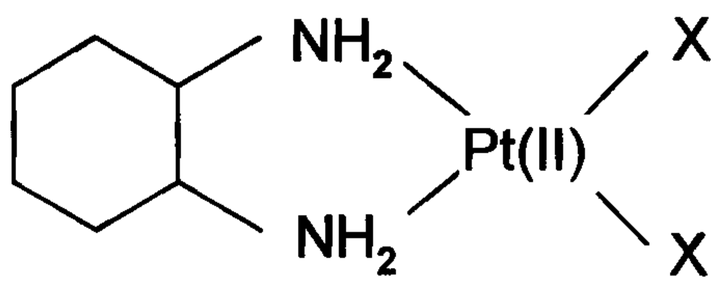
agitated for 8 hours at 45 degrees C. The suspension is subsequently cooled within 6 hours at 6 degrees C and filtered.

Di-ammonium oxalate monohydrate (20.19 g) is dissolved in water (278 mL). Water (3333 mL), ammonium oxalate solution and platinum-containing solution are combined and agitated for 8 hours at 45 degrees C. Subsequently activated carbon is added (3.05 g) and again further agitated for 16 hours. It is filtered and the active carbon treatment is repeated. The obtained solution is then led through a sterile filter into a rotary evaporator and concentrated at 55 to 65 degrees C in a vacuum to about 110 ml. The obtained suspension is filtered and the deposit is agitated thrice in water (28 ml) for 10 min. Subsequently it is washed thrice with methanol (139 ml). The filtered deposit is dried in sterile air stream for at least 24 hours. Yield of oxalato (*trans*-1-1,2-diaminocyclohexane) platinum (II) : 33.88 g (80%).

CLAIMS

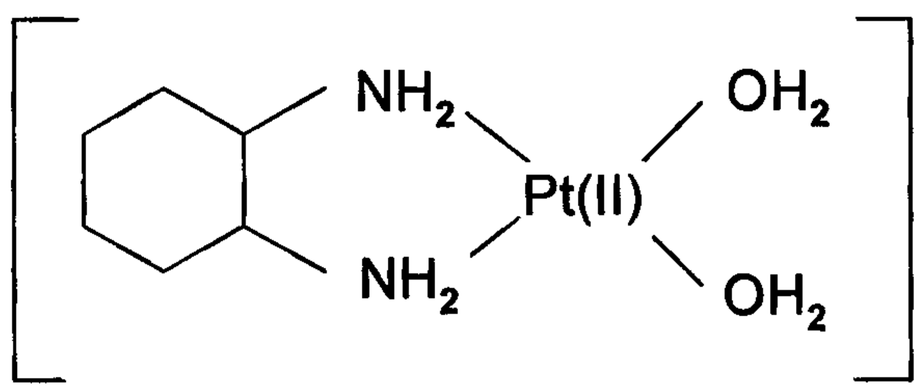
1. A process for the preparation of diaminocyclohexane-platinum(II)-dicarboxylates in an aqueous solution comprising the steps of:

B reacting $K_2PtX_4$ with 1,2-diaminocyclohexane (DACH) to form a compound of formula (2);




(2)

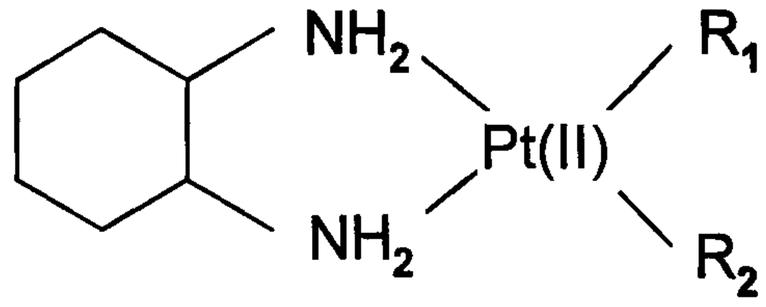
C reacting the compound of formula (2) with a silver salt $Ag_nA$ to form an intermediate of formula (3)




$A_n$ (3)

and removing the resulting AgX precipitate;

D reacting the intermediate of formula (3) with a dicarboxylate to form a compound of formula (1); and




(1)

F isolating the compound of formula (1),

wherein $R_1$ and $R_2$ together form a dicarboxylato group, X represents Cl or I, A represents a mono- or divalent anion of a mineral acid and n is 1 or 2,

characterized in that in step C a less than stochiometric amount of silver salt is used.

2. The process of claim 1 wherein X is I and the dicarboxylate is oxalate.

3. The process of claim 2 which further comprises the following preceding step:

A reaction of $K_2PtCl_4$ with KI to form $K_2PtI_4$.

4. The process of any one of claims 1-3 characterized by the fact that in step C the mixture is cooled to less than 10 degrees C before the removal of the precipitate.

5. The process of any one of claims 1-4 characterized by the fact that in step D ammonium oxalate is used.

6. The process of any one of claims 1-5 characterized by the additional step wherein the aqueous solution derived after step D

E is purified twice and filtered with activated carbon.

7. The process of claim 6 characterized by the additional step wherein the aqueous solution derived after step D or E is concentrated to less than 10 ml/g product.

8. The process of claim 6 characterized by the additional step wherein the aqueous solution derived after step D or E is concentrated to less than 10 ml/g product

9. The process of any one of claims 1-8 characterized by the fact that the aqueous solution is prepared using purified water as defined in European Pharmacopeia, 4$^{th}$ edition, 2002.

10. The process of claim 9 whereby the aqueous solution is prepared using highly purified water as defined in European Pharmacopeia, 4th edition, 2002.

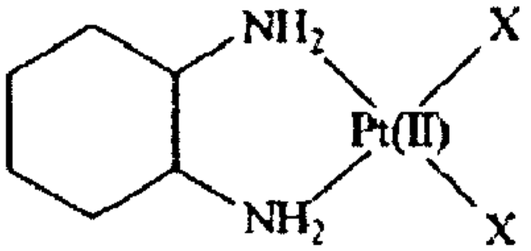
11. The process of claim 6 characterized by the additional step wherein the aqueous solution derived after step E) is sterilely filtered and then concentrated and the further additional step wherein

F the solid content is filtered and dried.

12. The process of claim 11 characterized by the additional step wherein

G the product of step F is washed with purified water or highly purified water and subsequently washed with a low boiling solvent that is pharmacologically acceptable.

13. Process in accordance with claim 12 whereby the solvent is methanol.

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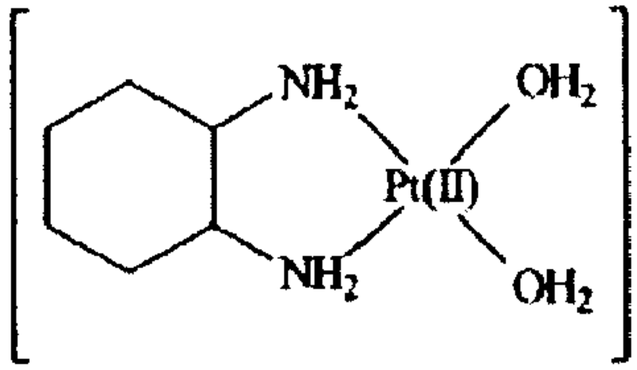


$A_n$

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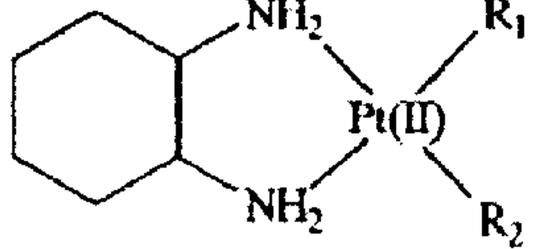


(1)