Title: PROCESS FOR THE PREPARATION OF ALOE-EMODIN

Abstract: Process for the preparation of aloe-emodin from aloin comprising oxidizing aloin by treatment with an oxygen containing gas, in an acid reaction medium, in the presence of a copper salt catalyst.
1

PROCESS FOR THE PREPARATION OF ALOE-EMODIN

The present invention relates to a process for preparing aloe-emodin by oxidation of aloin.

Aloe-emodin is a well-known compound widely used as an intermediate in the preparation of a number of therapeutically active compounds such as rhein and diacerein, for example as described in US 5,652,265 and EP0928781, and certain anthracyclines, for instance doxorubicin and related compounds as described in US 4,215,062.

Aloe-emodin and derivatives thereof have also been described for use in the treatment of cancer. For instance, EP1289513 describes the use of aloe-emodin in the treatment of neuroectodermal tumours. Use of aloe-emodin as an inhibitor of angiogenesis is described in WO2004/058185. Aloe-emodin has also been described for the treatment of psoriasis, for instance as in US 5,852,060, and for the treatment of the symptoms associated with burns, for instance as in DE 3,447,953, amongst others.

In the literature, there have been described a number of different processes for the preparation of aloe-emodin by semi-synthetic preparative processes starting from aloin, sennosides, chrysophanol, or by organic synthesis.

Processes starting from aloin are the most known, and numerous examples of the preparation of aloe-emodin from aloin have been described in the literature. The most used processes for preparing aloe-emodin from aloin involve the oxidation of aloin by iron (III) chloride using an acid catalyst to obtain aloe-emodin.

For example, US 5,652,265 describes the oxidation of aloin by means of iron (III) chloride with a hydrochloric acid catalyst, or with iron (II) sulphate using a sulphuric acid catalyst. In the process of US 5,652,265 the ferric salt is required in large quantities to carry out the oxidation. A ratio of ferric salt to aloin of 5:1 to

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15:1 w/w is described. CN 1810759 describes an alternative process in which aloin is refluxed with hydrochloric acid and then treated with a solution of aluminium (III) chloride in hydrochloric acid.

In WO 2006/051400 there is described a process for the preparation of aloe- emodin from aloin whereby aloin is oxidized to aloe- emodin by treatment with an oxygen-containing gas in a polyalcohol, in the presence of an acid.

In view of the increasing demand for aloe- emodin in the pharmaceutical field, there is an ongoing demand for the development of processes for the preparation of aloe- emodin, which are economical and can be easily applied on an industrial scale.

After extensive studies, the present inventors have found that aloe- emodin may be easily and advantageously prepared from crude aloin, without the need for chromium compounds or other toxic or harmful reagents, using a process which is simple, economical and can be easily scaled up to industrial level. The present invention has been achieved on a basis of these results.

Objects of the present invention are achieved by a process for preparing aloe- emodin according to claim 1.

Disclosed herein is a process for preparing aloe- emodin from aloin comprising oxidation of aloin by treatment with an oxygen-containing gas in an acidic reaction medium in the presence of a copper salt catalyst.

The process of the present invention comprises oxidation of aloin represented by the following formula (I):
To obtain aloe-emodin represented by the following formula (II):

The aloin is oxidized by treatment with an oxygen-containing gas in an acid reaction medium, in the presence of a copper salt catalyst.

The process of the invention advantageously provides effective oxidation of aloin, even from a starting material aloin having a low degree of purity.

The aloin starting material may have a purity of from 1% to 100%. Accordingly as the starting material may be used pure aloin, commercially available aloin (for example in the form of aloe stone) or crude aloin, preferably crude aloin in the form of an extract from different plant species containing at least 1% of aloin.

The process of the present invention advantageously enables the preparation of aloe-emodin at a good yield and with satisfactory purity from crude aloin containing from 5% to 20% pure aloin. Particularly, crude aloin having a purity of 5 to 20%, as extracted from aloe-species, for example acibar the extract of aloe-
vera without any purification or treatment, may be advantageously used as starting material. Such crude aloin is widely commercially available and inexpensive.

Aloin may also be used in the form a solid aloin, e.g. having a purity of aloin from 20% to 100%. Particularly, commercially available forms of aloin may be envisaged, such as aloe stone, containing for example from 20% to 40% pure aloin.

The use of crude aloin extracted from aloe species containing from 5% to 20% pure aloin is particularly advantageous from the point of view of production costs.

The oxidation reaction is carried out in an acidic reaction media. The acid reaction media preferably comprises one or more mineral acids, and may be for example hydrochloric acid or sulphuric acid. Preferably 0.5 M to 6.0 M hydrochloric acid or sulphuric acid may be used. In a preferred embodiment the oxidation is carried out in hydrochloric acid.

The oxidation of aloin is carried out in the presence of a copper salt catalyst, particularly a copper (I) salt or copper (II) salt. Examples of suitable copper salts include specifically, but not exclusively, chloride, sulphate, bromide or nitrate salts. Preferably, chloride or sulphate salts of copper are used, particularly copper (I) chloride or copper (II) chloride. The copper salt compound is used in a catalytic amount ranging from 0.5% to 30% w/w with respect to aloin. Preferably the copper salt catalyst compound is used in an amount of from 1.5% to 5.0% w/w with respect to aloin.

In a preferred embodiment of the present invention, the oxidation is carried out at a temperature in the range from 40°C to 125°C, more preferably at a temperature in the range from 80°C to 90°C.

The aloin starting material may be suspended in the acid reaction medium at room temperature and then dissolved by heating. Alternatively the acid reaction
medium may be preheated before addition of the aloin. No organic solvents are 
required for dissolution of the aloin, and the oxidation of aloin is advantageously 
carried out in the absence of organic solvent.

Oxidation of the aloin is carried out by active treatment with an oxygen-containing 
gas. The reaction mixture comprising the aloin starting material in an acid reaction 
media is subjected to a gas over-pressure of an oxygen-containing gas in the 
presence of the copper salt catalyst. Preferably the oxidation of aloin may be 
carried out by introducing the oxygen-containing gas in a continuous way into the 
heated reaction mixture, or may be performed in a pressure reactor.

According to one embodiment of the present invention, aloin is suspended in the 
acid reaction medium with the copper salt catalyst, the reaction mixture is heated 
to the reaction temperature, and the oxygen-containing gas is then bubbled in a 
continuous way into the heated solution until the reaction is completed. The 
degree of conversion to aloe-emodin, and completion of the reaction, may be 
determined by conventional analysis techniques, for example by HPLC analysis. 
Oxygen gas or air is preferably introduced into the heated solution at a flow rate of 
about 5-50 L/hour, more preferably about 15-30 L/hour. The time required for 
completion of the reaction depends on the oxygen-containing gas flow rate and on 
the oxygen concentration of the oxygen-containing gas. The oxidation may be 
usually be carried out over about 3-12 hours, generally about 5-7 hours.

Where oxidation of aloin is carried out in a pressure reactor, the heated reaction 
mixture is added to the reaction chamber, and then air or oxygen gas introduced 
into the reaction chamber to a pressure of about 1.0-5.0 bar absolute pressure. 
The pressure is maintained by oxygen-containing gas addition until constant 
pressure is observed. Where oxygen gas is used, the reaction is suitably carried 
out under a gas pressure of about 1.2-2.5 bar, for example around 2 bar. If the 
oxidation is carried out using air as the oxygen-containing gas, the reaction is 
preferably carried out under a gas pressure of about 1.2-10 bar absolute pressure, 
preferably 2-5 bar.
The aloe-emin containing oxidation product residue may be separated from the reaction mixture by filtration. The aloe-emin concentration in the oxidation-product solid residue depends largely on the purity of the starting aloin, generally ranging from about 20% to 60% w/w. For instance the oxidation of aloin containing 5%-20% pure aloin gives a residue that contains about 20% to 40% of aloe-emin, and the oxidation of aloin containing 90% to 95% pure aloin, gives an oxidation product residue containing up to 60% of aloe-emin. A conversion rate from aloin to aloe-emin of at least 65% may be obtained starting from aloin having a purity as low as 5%.

The reaction time will depend on the reaction conditions, amongst others on the concentration of oxygen in the oxygen-containing gas and on the gas pressure applied. The oxidation of aloin by treatment with an oxygen-containing gas in a pressure reactor may generally be carried out over 3-15 hours, for instance 6-12 hours.

The oxidation reaction will usually be followed by a conventional treatment of the aloe-emin containing reaction product residue, to isolate the crude aloe-emin. Recovery of the aloe-emin may, for example, be carried out by extraction using an organic solvent, such as toluene or dichloromethane. For instance, aloe-emin may be extracted by soxhlet or nutcha filter using toluene or dichloromethane as solvent.

The crude aloe-emin may be recovered at more than 85% with an aloe-emin purity of at least 75%. If desired the extraction of crude aloe-emin product may be followed by purification of the crude aloe-emin by conventional processes, e.g. by crystallization, to obtain aloe-emin in pure form.

Advantageously the mother liqueurs from the oxidation reaction, i.e. the filtrate, containing acid and copper salt catalyst, obtained in the filtration of the aloe-emin containing oxidation product residue after completion of the oxidation,
may be re-used directly, without any treatment or purification, as reaction media for subsequent oxidation reactions of aloin to aloe-emodin. For instance, the initial acid and copper salt catalyst can be re-used in 1 to 10 further oxidations. The initial acid and copper salt catalyst used in a first oxidation reaction can be advantageously be re-used in up to 4 further oxidations of aloin to aloe-emodin without significant reduction in aloe-emodin yield. The re-use of the acid and the copper salt catalyst in this way provides clear economical and environmental benefits.

The aloe-emodin produced by the process of the present invention may advantageously be used in the production of rhein and diacerein.

According to the process of the present invention, aloe-emodin may be obtained at a good yield and good level of purity from crude aloin having a purity as low as 5%.

The process according to the invention is also economical since crude aloin having a purity of 5% to 20% aloin may be used as the starting material, inexpensive reagents may be used in the process, and further since the acid reaction medium and copper salt catalyst may be re-used in multiple oxidations.

Moreover the process of the present invention is simple and easy to carry out even on an industrial scale.

The present invention is further illustrated by the following non-limiting examples.

**Examples**

**Example 1: Oxidation of Aloin 30 (HPLC 31 % aloin)**

(I) 1L of HCl 3M was poured into a reaction flask and 70g of aloin 30 (Laboratoire Medidom, Switzerland) (31% of aloin) was added over 5 minutes at room
temperature (20-25 °C) with vigorous stirring. The mixture was stirred for 20 minutes and then was heated for one hour at 80 °C. 3.5 g copper (I) chloride was added and a gas diffuser was introduced into the solution. Oxygen gas was introduced at a flow rate of 30 L/h. The mixture was heated at 90 °C for 7 hours with continuous oxygen gas flow and stirring. A dark brown solid was formed.

The oxygen gas flow was stopped and the gas diffuser was removed. The resulting suspension was cooled at room temperature overnight. The solid product was filtered and washed with 25 - 30 ml of HCl 3M (the mother liqueurs were retained). The dark brown solid product residue was washed with water (200 - 300 ml). 33.6g of brown solid product residue was obtained, containing 30.0% of Aloe-emodin. 72% yield.

The mother liqueurs were used in four successive operations:

(2) The mother liqueurs of the 1st oxidation were poured into the flask and 70g aloin 30 (31% aloin) added as in (I) above. The oxidation was carried out as in (I). 37.9 g of brown solid was obtained, containing 27.0% of aloe-emodin. 73% yield.
(3) The mother liqueurs of the 2nd oxidation were poured into the flask and 70g aloin 30 (31% aloin) added as in (I) above. The oxidation was carried out as in (I). 39.0 g of brown solid was obtained, containing 25.3% of aloe-emodin. 70.4% yield.
(4) The mother liqueurs of the 3rd oxidation were poured into the flask and 70g aloin 30 (31% aloin) added as in (I) above. The oxidation was carried out as in (I). 44.3 g of brown solid was obtained, containing 21.0% of aloe-emodin. 66.4% yield.
(5) The mother liqueurs of the 4th oxidation were poured into the flask and 70g aloin 30 (31% aloin) added as in (I) above. The oxidation was carried out as in (I). 40.0 g of brown solid was obtained, containing 21.4% of aloe-emodin. 61.1% yield.

Extraction (Soxhlet type)
The extractor body was prepared and the pooled solid residues (194g) were added. Toluene (1400g) was added into the flask and the system was refluxed for 16-20 hours. An orange solid was formed. The mixture was cooled at room temperature and the solid filtered and washed with toluene (100g).

55.3g of aloe-erodin was obtained as an orange solid, yield 92%, aloe-erodin purity 80%.

Example 2: Oxidation of Acibar (Aloin HPLC 5.1 %)

(1) 0.7L of HCl 5M was poured into a reaction flask and then 350g acibar (Laboratoire Medidom, Switzerland) (5.11% of aloin) was added over 5 minutes at room temperature (20-25 °C) with vigorous stirring. The mixture was stirred for 20 minutes and then was heated for one hour to 80 °C. 5.0g copper (I) chloride was added and a gas diffuser was introduced into the flask. Oxygen gas was introduced at a flow rate of 30 L/h. The mixture was heated at 90 °C for 7 hours with continuous oxygen gas flow and stirring. A dark brown solid was formed. The gas diffuser was removed and oxygen gas addition was stopped. The resulting suspension was cooled at room temperature overnight. The solid product was filtered and washed with 25 - 30 ml of HCl 3M (the mother liqueurs were retained). The dark brown product residue solid was washed with water (150 - 230 ml).

22.2g of a brown solid was obtained containing 33.8 % of aloe-erodin. 65% yield.

The mother liqueurs were used in two successive operations:

(2) The mother liqueurs of the 1st oxidation were poured into the flask and 327g acibar (5%-11% aloin) was added. The oxidation reaction was carried out as above. 24.3 g of brown solid was obtained, containing 30.4% of aloe-erodin. 68.6% yield.

(3) The mother liqueurs of the 2nd oxidation were poured into the flask and 327g acibar (5%-11% aloin) was added. The oxidation reaction was carried out as above. 25.6 g of brown solid was obtained, containing 27.7% of aloe-erodin. 65.9% yield.
Example 3: Oxidation of Aloin 90 (HPLC 90%)

1L of HCl 3M was poured into a reaction flask and 70g aloin 90 (Laboratoire Medidom, Switzerland) (90% purity aloin) was added over 5 minutes at room temperature (20-25 °C) with vigorous stirring. The mixture was stirred for 20 minutes and then was heated in one hour at 80 °C. 3.5g copper (I) chloride was added and a gas diffuser was introduced into the flask. Oxygen gas was introduced at a flow rate of 30 L/h. The mixture was heated at 90 °C for 7 hours with continuous oxygen gas flow and stirring. A dark brown solid was formed.

The gas diffuser was removed and oxygen gas flow stopped. The resulting suspension was cooled at room temperature overnight. The suspension was filtered and the solid residue washed with 25 - 30 ml of HCl 3M (the mother liqueurs were retained). The dark brown solid product residue was washed with water (200 - 300 ml). 45.6 g of brown solid was obtained containing 63% of aloe- emodin. 70.8% yield

Example 4: Oxidation of Aloin 30 (HPLC 31%) under pressure

Under a nitrogen atmosphere, 1L of HCl 3M was poured into the pressure reactor and 70g aloin 30 (Laboratoire Medidom, Switzerland) (31% of aloin) was added over 5 minutes at 20 – 25 °C with vigorous stirring. The mixture was stirred for 20 minutes and 3.5g copper (I) chloride was added. The reactor was heated in one hour to 90 °C and then was pressurised by the introduction of oxygen gas up to a pressure of 2 bars absolute pressure. The pressure was maintained for 10 hours by additions of oxygen gas. The reactor was depressurised and then was cooled at room temperature overnight. The solid product was separated by filtration and washed with 25 - 30 ml of HCl 3M. The dark brown solid product residue was washed with water (200 - 300 ml).

33.0g of brown solid was obtained, containing 29.5% of aloe-emodin. 70% yield.
Claims

1. A process for the preparation of aloe-erodin from aloin comprising oxidizing aloin by treatment with an oxygen containing gas, in an acid reaction medium, in the presence of a copper salt catalyst.

2. A process according to claim 1 wherein the copper salt is a copper (I) salt or a copper (II) salt selected from the group consisting of chloride, bromide, or sulphate salts.

3. A process according to claim 1 or 2 wherein the copper salt is copper (I) chloride or copper (II) chloride.

4. A process according to any one of claims 1 to 3 wherein the copper salt catalyst is present in an amount of from 0.5% to 30% w/w with respect to the aloin.

5. A process according to any one of claims 1 to 4 wherein the aloin is crude aloin extracted from plants, having a purity of more than 1%.

6. A process according to claim 5 wherein the aloin is crude aloin having a purity of 5% to 20%.

7. A process according to any one of claims 1 to 5 wherein the acid reaction media is selected from hydrochloric acid or sulphuric acid.

8. A process according to any one of claims 1 to 7 wherein the treatment with an oxygen-containing gas is performed by flowing an oxygen-containing gas through the reaction mixture.

9. A process according to any one of claims 1 to 7 wherein the oxidation is performed in a pressure reactor under a pressure of oxygen-containing gas of 1.2 to 5.0 bars.
10. A process according to any one of claims 1 to 9 wherein the oxygen-containing gas is selected from oxygen gas or air.

11. A process according to any one of claims 1 to 10 wherein the oxidation is performed at a temperature ranging from 80 °C to 90 °C.

12. A process according to any one of claims 1 to 11 wherein the aloe-emodin oxidation reaction product is recovered by filtration and a filtrate obtained from this filtration, comprising acid and copper salt catalyst, is re-used in a subsequent oxidation of aloin to aloe-emodin.

13. A process according to claim 12 wherein the filtrate comprising acid and copper salt catalyst is re-used 1 to 4 times.
## A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C46/02

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)

C07C

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)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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### INTERNATIONAL SEARCH REPORT

**Information on patent family members**

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