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(54) A process for the isolation of (+)-usnic acid from usnea barbata L

(57) A process for the direct and simple isolation of (+)-usnic acid, which due to its biocide activity is useful in pharmacy and cosmetics, from *Usnea barbata L.* by means of extraction with ethanol as extraction solvent, followed by filtration under pressure or in vacuo, is disclosed.

This print takes account of replacement documents later filed to enable the application to comply with the formal requirements of the Patents Rules 1978.

SPECIFICATION

A process for the isolation of (+)-usnic acid from *Usnea barbata L.*

The present process relates to the isolation of (+)-usnic acid from *Usnea barbata L.* Usnic acid is a known substance, which, due to its biocide action, is used in pharmacy and cosmetics.

At the isolation of (1)-usnic acid from moss and lichen, problems of the choice of raw materials, of the optimum solvent and of the optimum isolation process have to be dealt with.

It is well known that for the preparation of (+)-usnic acid different kinds of moss and lichen can be used, e.g. *Evernia prunastri, Usnea barbata L., Ramalina reticulata* etc. The choice of raw materials depends above all upon the following requirements:—

that said materials are available in amounts sufficient for industrial use,

that the content of usnic acid therein justifies an economical production (over 1%),

that the content of accompanying extractive substances therein is not significant with reference to the content of (+)-usnic acid,

that the solubility of accompanying extractive substances in the extraction solvent used is considerably lower than that of (+)-usnic acid.

Usnea barbata L. almost fully meets said requirements and is used for the isolation of (+)-usnic acid according to the process which is the subject of the present application. Other kinds of lichen contain considerably less (+)-usnic acid or are preferably used as raw materials for obtaining perfurmed resins (resinoids).

A solvent for the isolation of (+)-usnic acid must fulfil the following requirements:—

that thereby (+)-usnic acid is extracted as selectively as possible with reference to the accompanying extractive substances,

that the maximum yield can be achieved,

that such a quality of the isolated substance is provided, which meets all requirements for its use as antibioticum and fungicide, especially from the physiological point of view,

that it does not alter the antibiotic and fungicide properties of the (+)-usnic acid,

that a simpler and more economical production is made possible,

that it is not expensive and is available in sufficient amounts,

that it is not toxic or inflammable so as to require costly equipment.

The isolation process should meet the following requirements:—

it must be simple,

it must provide the maximum yield and quality,

it should not require costly and complicated equipment,

it should require as little working power, energy and time as possible.

In Prior Art there is disclosed only a small number of processes for the isolation of (+)-usnic acid from different kinds of moss and lichen. In most known processes (+)-usnic acid is obtained from the waxy residue after separating perfumed components. Vegetable raw materials used contain (+)-usnic acid is considerably smaller amounts than *Usnea barbata L.* Therefore and because perfumed resins can be isolated in a much better yield, the isolation of (+)-usnic acid therefrom is of secondary improtance. Main features of said prior art processes are as follows:—

application of two or more organic solvents,

application of solvents which are physiologically toxic, such as acetone, benzene, chloroform, 1,1,2-trichloroethylene, hexane etc., and thus have to be completely removed from the crystals of (+)-usnic acid,

smaller yields of (+)-usnic acid as several purification procedures are necessary for achieving a satisfactory quality,

difficulties in regenerating particular solvents,

complicated production (many purifications, regeneration of several solvents, use of sophisticated equipment),

ethanol, which is one of the best available and most suitable extraction solvents from the technical and physiological point of view, is not applied,

impossibility of direct crystallization of (+)-usnic acid of a satisfactory quality from the solution of waxy residue because of considerable solubility of accompanying substances in solvents used,

from an economical point of view prior art processes are very expensive for the preparation of (+)-usnic acid on an industrial scale.

So far there have been disclosed only few processes for obtaining (+)-usnic acid from *Usnea barbata L.* Their characteristics are almost the same as those of processes for obtaining (+)-usnic acid from waxy residues of resinoids.

It is well known that pure (+)-usnic acid is soluble in ethanol. Its solubility in ethanol, however, is much smaller when compared with that in the solvents recommended for extraction in Prior Art processes (acetone, chloroform, ethyl acetate, benzene). Therefore ethanol has not been considered as a possible extracting agent for (+)-usnic acid till now. Surprisingly, the results of our research according to the present invention have shown that ethanol is an optimum solvent for obtaining (+)-usnic acid though it is known that pure (+)usnic acid is only weakly soluble therein.

In Prior Art there has not been laid enough importance upon this fact and, consequently, ethanol has never been applied as extraction solvent for (+)-usnic acid. Namely, the solubility of a chosen substance in a chosen solvent can be increased or reduced due to the presence of other extractive substance from a vegetable raw material in an extract.

Ethanol is advantageous over other Prior Art solvents in the following:—

the solubility of (+)-usnic acid in ethanolic extract of *Usnea barbata L.* is increased in the presence of accompanying extractive substances contained in the vegetable raw material, the amount of extracted accompanying extractive substancss in ethanol is small so that (+)-usnic acid can crystallize directly from the ethanolic extract as pure substance and in good yield (about 85 to 90% with reference to the content in the vegetable raw material),

the solubility of (+)-usnic acid at the boiling point of ethanol is considerably greater than that of accompanying extractive substances,

the solubility of (+)-usnic acid is very poor at its crystallization temperature (under +15°C), whereas that of accompanying substances is still very good and thus (+)-usnic acid crystallize with very small amounts of impurities,

the solubility of (+)-usnic acid in Prior Art extraction solvents is considerably greater, but that of accompanying substances is much greater too and direct crystallization from extract is thus rendered impossible, which is not the case when ethanol is used.

Prior Art processes are e.g. the following:—

a) Vestnik Akad. Nauk S.S.S.R. 26, No. 7, 35—7 (1956) (+)-usnic acid is isolated by extraction from lichen with hot benzene, benzene is evaporated, the residue is treated with very little hot chloroform, the chloroform solution is evaporated and the residue is treated with its triple weight of cold ethanol. Thus obtained (+)-usnic acid is purified by successive dissolution in hot chloroform, cold ethanol and ether.

b) French Patent Application No. 76 11964 relates to a process for extracting (+)-usnic acid from waxy residue of abs. extraction of lichens. The waxy residue is extracted with solvents, such as benzene, hexane, acetone, chloroform or 1,1,2-trichloro-ethylene. The obtained solution is heated to boiling, filtered and cooled, whereafter (+)-usnic acid crystallizes. The yield of (+)-usnic acid is 20—25% with benzene and 35—40% with hexane.

c) Rumanian Patent Specification No. 58,246 (+)-usnic acid is extracted three times from *Usnea barbata L.* by means of benzene under reflux, combined extracts are evaporated to a small volume and from the concentrated solution (+)-usnic acid is precipitated with acetone.

According to the present process, after the removal of dust the drug is extracted with ethanol under reflux. The obtained extract is filtered and transferred into the crystallization vessel. The crystallization is carried out under external cooling of the tank and the stirring of the solution. Fine yellow crystals of (+)-usnic acid are separated by filtering under pressure (2.10^5 Pa to 3.10^5 Pa) or *in vacuo* (2.7.10^3 Pa to 13.3.10^3 Pa), washed with cold ethanol and dried. Ethanol is regenerated from the filtrate by column distillation.

The process according to the invention substantially differs from Prior Art Processes and has the following essential advantages over said processes:—

a rapid and simple extraction process,

the use of only one solvent,

as the optimum solvent for the extraction of (+)-usnic acid from *Usnea barbata L.* ethanol is applied for the first time, though it is well known that pure usnic acid is very weakly soluble therein,

the application of ethanol is advantageous over Prior Art solvents from a technical and physiological point of view (it is readily available, possible residues in crystals need not be removed, it is less dangerous for industrial use and less toxic),

direct crystallization of (+)-usnic acid from the ethanolic extract without previous concentrating,

high yield of (+)-usnic acid (over 90% with reference to the content in the raw material),

by the high quality of (+)-usnic acid obtained by direct crystallization from ethanolic extract, there is avoided any additional purification, which is necessary in Prior Art process,

the possibility of regeneration of the solvent for over 90%,

simple production plant,

the present process is much more economical in comparison with known processes.

The following Examples are given for a better explanation of the present process without limiting the scope thereof.

Example 1

100 kg of *Usnea barabata L.*, after removal of dust, are extracted under reflux for 30 minutes with 800 kg of ethanol (96%, pharm. grade). After filtering through a steel net the extract is introdcued into a crystallization tank with water cooling, wherein (+)-usnic acid crystallizes during 8 hours under stirring. Crystals of (+)-usnic acid are separated by filtering under pressure (2.10^5 Pa to 3.10^5 Pa) or *in vacuo* (2.7.10^3 Pa to 13.3.10^3 Pa), washed with ethanol and dried.

90—95% of ethanol is regenerated from the filtrate by evaporation.

The yield of (+)-usnic acid in crystals is 90% with regard to the content in the vegetable raw material. The content of (+)-usnic acid/m.p. 204°C; $[\alpha]^{25}_{D}$+498 (in chloroform)/in crystals is 98% with regard to the dry substance.

Example 2

100 kg of *Usnea barbata L.* are treated as in Example 1 with the exception that the extraction time is 60 minutes, the amount of ethanol for extraction is 1200 kg and the crystallization time is 12 hours. The yield of (+)-usnic acid in crystals is 90% with reference to the content in the vegetable raw material. The content of (+)-usnic acid/m.p. 204°C; $[\alpha]^{25}_{D}$+498 (in chloroform)/in crystals is 96% with regard to the dry substance.

Claims

1. A process for the isolation of (+)-usnic acid from *Usnea barbata L* characterized in that *Usnea barbata L.* after removal of dust is extracted with ethanol in the ratio from 1:8 to 1:12 under reflux, the extract is separated from the drug by filtration under pressure from 2.10^5 to 3.10^5 Pa or *in vacuo* from 2.7.10^3 to 13.3.10^3 Pa, crystallized under

stirring, the crystals separated by filtration, washed with ethanol and dried.

2. A process for the isolation of (+)-usnic acid from *Usnea barbata L.* substantially as hereinbefore described in Examples 1 or 2.

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